

## Issue Overview

### **Sleep Neurology 2017;23(4)**

*Continuum: Lifelong Learning in Neurology*® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

### **Learning Objectives**

Upon completion of this *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue, participants will be able to:

- Discuss the brain mechanisms that control sleep and wakefulness, and recognize how the breakdown of these mechanisms contributes to common disorders and disturbances of sleep
- Describe a clinical approach to the appropriate investigation and diagnosis of sleep disorders commonly seen by neurologists
- Recognize clinical features, recall the diagnostic criteria, discuss the latest advances in the understanding of the pathophysiology, and manage narcolepsy and other central hypersomnias
- Discuss the epidemiology, pathophysiology, and treatment of restless legs syndrome and other sleep-related movement disorders
- Diagnose and manage idiopathic and secondary rapid eye movement (REM) sleep behavior disorder, discuss the recent advances regarding idiopathic REM sleep behavior disorder as a primary feature of a synuclein disease, and recognize the typical features of sleep paralysis and nightmares
- Discuss the pathophysiologic basis of non-REM and overlap parasomnias, and appropriately diagnose and manage them in the clinical setting

- Describe the physiology of circadian rhythms and the relationships between circadian rhythms and neurologic disorders (including epilepsy and dementia), and diagnose the common circadian rhythm sleep-wake disorders, including delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, and irregular sleep-wake rhythm disorder
- Define insomnia, particularly as it presents in routine neurologic practice; recognize the evolution of insomnia and its pathophysiology; and use diagnostic tools and specific intervention techniques for insomnia, including behavioral approaches and pharmacologic options
- Discuss the prevalence, pathophysiology, diagnostic criteria, evaluation, and treatment of sleep-disordered breathing and its impact on medical and neurologic comorbidities
- Recognize sleep disturbances associated with common neurologic disorders, and describe the general approach to their management
- Discuss the diagnosis and management of childhood sleep-wake disorders
- Discuss strategies of shared medical decision making between the clinician and patient
- Recognize patients with neurologic disorders at increased risk for motor vehicle crashes and determine their fitness to drive

#### Core Competencies

This *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue covers the following core competencies:

- Patient Care
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

## Disclosures

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*<sup>b</sup>Dr St. Louis discusses the off-label use of clonazepam and melatonin for the treatment of rapid eye movement sleep behavior disorder.*

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*<sup>b</sup>Dr Trotti discusses the unlabeled/investigational use of benzodiazepines, botulinum toxin, clonazepam, and clonidine for the treatment of bruxism; of clonazepam for the treatment of hypnic myoclonus and rhythmic movement disorder; of carbamazepine, carisoprodol, diltiazem, gabapentin, lamotrigine, magnesium, oxcarbazepine, quinine, and verapamil for the treatment of leg cramps; of clonazepam and topiramate for the treatment of propriospinal myoclonus; and of gabapentin, iron (including ferric carboxymaltose), opioids, and pregabalin for the treatment of restless legs syndrome.*

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**Methods of Participation and Instructions for Use**

*Continuum: Lifelong Learning in Neurology*® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills. In *Continuum*, the process of absorbing, integrating, and applying the material presented is as important as, if not more important than, the material itself.

The goals of *Continuum* include disseminating up-to-date information to the practicing neurologist in a lively, interactive format; fostering self-assessment and lifelong study skills; encouraging critical thinking; and, in the final analysis, strengthening and improving patient care.

Each *Continuum* issue is prepared by distinguished faculty who are acknowledged leaders in their respective fields. Six issues are published annually and are composed of review articles, case-based discussions on ethical and practice issues related to the issue topic, coding information, and comprehensive CME and self-assessment offerings, including a self-assessment pretest, multiple-choice questions with preferred responses, and a patient management problem.

For detailed instructions regarding *Continuum* CME and self-assessment activities, visit [aan.com/continuum/cme](http://aan.com/continuum/cme).

The review articles emphasize clinical issues emerging in the field in recent years. Case reports and vignettes are used liberally, as are tables and illustrations. Video material relating to the issue topic accompanies issues when applicable.

The text can be reviewed and digested most effectively by establishing a regular schedule of study in the office or at home, either alone or in an interactive group. If subscribers use such regular and perhaps new study habits, *Continuum*'s goal of establishing lifelong learning patterns can be met.

# Sleep Neurology

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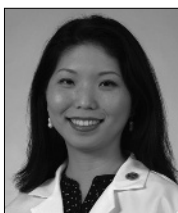
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*<sup>b</sup>Dr Trotti discusses the unlabeled/investigational use of benzodiazepines, botulinum toxin, clonazepam, and clonidine for the treatment of bruxism; of clonazepam for the treatment of hypnic myoclonus and rhythmic movement disorder; of carbamazepine, carisoprodol, diltiazem, gabapentin, lamotrigine, magnesium, oxcarbazepine, quinine, and verapamil for the treatment of leg cramps; of clonazepam and topiramate for the treatment of propriospinal myoclonus; and of gabapentin, iron (including ferric carboxymaltose), opioids, and pregabalin for the treatment of restless legs syndrome.*



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# CONTINUUM

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# Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue, participants will be able to:

- ▶ Discuss the brain mechanisms that control sleep and wakefulness, and recognize how the breakdown of these mechanisms contributes to common disorders and disturbances of sleep
- ▶ Describe a clinical approach to the appropriate investigation and diagnosis of sleep disorders commonly seen by neurologists
- ▶ Recognize clinical features, recall the diagnostic criteria, discuss the latest advances in the understanding of the pathophysiology, and manage narcolepsy and other central hypersomnias
- ▶ Discuss the epidemiology, pathophysiology, and treatment of restless legs syndrome and other sleep-related movement disorders
- ▶ Diagnose and manage idiopathic and secondary rapid eye movement (REM) sleep behavior disorder, discuss the recent advances regarding idiopathic REM sleep behavior disorder as a primary feature of a synuclein disease, and recognize the typical features of sleep paralysis and nightmares
- ▶ Discuss the pathophysiologic basis of non-REM and overlap parasomnias, and appropriately diagnose and manage them in the clinical setting
- ▶ Describe the physiology of circadian rhythms and the relationships between circadian rhythms and neurologic disorders (including epilepsy and dementia), and diagnose the common circadian rhythm sleep-wake disorders, including delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, and irregular sleep-wake rhythm disorder
- ▶ Define insomnia, particularly as it presents in routine neurologic practice; recognize the evolution of insomnia and its pathophysiology; and use diagnostic tools and specific intervention techniques for insomnia, including behavioral approaches and pharmacologic options
- ▶ Discuss the prevalence, pathophysiology, diagnostic criteria, evaluation, and treatment of sleep-disordered breathing and its impact on medical and neurologic comorbidities
- ▶ Recognize sleep disturbances associated with common neurologic disorders, and describe the general approach to their management
- ▶ Discuss the diagnosis and management of childhood sleep-wake disorders
- ▶ Discuss strategies of shared medical decision making between the clinician and patient
- ▶ Recognize patients with neurologic disorders at increased risk for motor vehicle crashes and determine their fitness to drive

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## Core Competencies

This *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue covers the following core competencies:

- ▶ Patient Care
- ▶ Medical Knowledge
- ▶ Practice-Based Learning and Improvement
- ▶ Interpersonal and Communication Skills
- ▶ Professionalism
- ▶ Systems-Based Practice



# Whatcha Talkin' 'Bout, Willis-Ekbom?

In 2013, the Restless Legs Syndrome Foundation changed its name to the Willis-Ekbom Disease Foundation<sup>1</sup> based on the recommendation of an advisory group that suggested a name change for the condition.<sup>2</sup> The recommendation and decision were based on a number of factors, including recognition that the disorder is not always restricted to the legs, a response to a concern about trivialization of the disorder, an acknowledgment of its first known description by Sir Thomas Willis in 1672 and the detailed description in a case series by Karl Ekbom in 1945, and for ease of cross-cultural communication.<sup>1</sup> By 2015, based on “feedback from members, health care providers, and scientists” and recognition that the name *restless legs syndrome* continued to be used, the foundation reverted to the Restless Legs Syndrome Foundation.<sup>3</sup> The result is that *restless legs syndrome*, which had become *restless legs syndrome/Willis-Ekbom*

*disease* in the literature, is now typically initially referred to as “restless legs syndrome (also known as Willis-Ekbom disease),” with the parenthetical mention for clarification and recognition of its (arguably ephemeral) recent alternative name. So, in this issue we aren’t “talking about” Willis-Ekbom, aside from a parenthetical initial mention of the eponym.

The sleep literature has at least one other set of alternative terms for the same entity, that being *hypocretin* and *orexin* for the neurotransmitter whose deficiency is integral in the pathogenesis of narcolepsy type 1. In this case, the use of two terms for the same molecule is based on its near-simultaneous discovery by two groups: one that coined the term *hypocretin* because it is produced in the hypothalamus and resembles the hormone secretin,<sup>4</sup> and another that coined the term *orexin* while performing research related to obesity.<sup>5</sup> These two synonymous terms remain in ongoing use,<sup>6</sup> often occurring next to each other separated by a slash (*hypocretin/orexin*). In



I am very thankful to Guest Editor Dr Erik K. St. Louis for assembling a remarkable group of renowned sleep experts to guide us in the care of our many patients with disordered sleep, whether in the context of a primary sleep disorder or in the setting of another neurologic disorder.

*Continuum*, we have tended to continue that usage, although we admit to some variation (using either term or both terms with the slash mark) between articles and even within articles, according to the article authors’ original usage. Note that terminology issues are not restricted to any particular subspecialty, as in the “fibular nerve/peroneal nerve” nomenclature in the next issue of *Continuum*.

Back to this issue, I am very thankful to Guest Editor Dr Erik K. St. Louis for assembling a remarkable group of renowned sleep experts to guide us in the care of our many patients with disordered sleep, whether in the context of a primary sleep disorder or in the setting of another neurologic disorder. After reading this remarkable issue, which was so carefully crafted by Dr St. Louis and his team, I suspect that many readers will agree with me—on the subject

of language—that the intersection of sleep (a neurologic process), sleep disorders (themselves neurologic disorders), and other neurologic disorders makes the term *neurology* in the *Sleep Neurology* title of the issue reiterative.

The issue begins with an overview by Drs Richard L. Horner and John H. Peever of the fundamental anatomy and physiology controlling normal sleep and wakefulness, providing the background of how dysfunction in these circuits underlie many of the disorders described in the subsequent articles. Next, Dr Michael H. Silber provides a thorough introduction and overview of the indications for, and reasoning underlying, the diagnostic approaches and investigation of the many sleep disorders we encounter.

The issue then moves on to specific sleep disorder syndromes, starting with the article by Drs Yves Dauvilliers and Lucie Barateau, who review the current concepts of pathophysiology and diagnosis and management of narcolepsy and other central hypersomnias. Dr Lynn Marie



Trotti next reviews the pathophysiology, diagnosis, and current management recommendations for restless legs syndrome and other sleep-related movement disorders.

The issue proceeds to discussions of the rapid eye movement (REM) sleep and non-REM sleep parasomnias, beginning with the article by Drs Birgit Högl and Alex Iranzo, who review the diagnosis and management of REM sleep behavior disorder (and its prognosis as a frequent harbinger of an underlying synucleinopathy) and other REM sleep parasomnias. Drs Muna Irfan, Carlos H. Schenck, and Michael J. Howell discuss the diagnosis, differential diagnosis, evaluation, and management of the non-REM sleep parasomnias and overlap parasomnias.

Dr Milena Pavlova then discusses the physiology of endogenous circadian rhythms and the pathophysiology, diagnosis, and management of the circadian rhythm sleep-wake disorders. Drs Alon Y. Avidan and David N. Neubauer next review the diagnostic evaluation and management of our patients with the various causes of chronic insomnia disorder.

Drs Nancy R. Foldvary-Schaefer and Tina E. Waters next summarize the diagnostic criteria, evaluation, and management of the various causes of sleep-disordered breathing. Drs Yo-El S. Ju, Aleksandar Videnovic, and Bradley V. Vaughn then review the sleep disturbances that are comorbid with a number of other neurologic disorders, emphasizing that management of the sleep disturbance may improve the symptoms of the neurologic disease. In the final review article of the issue, Dr Suresh Kotagal reviews the diagnosis and management of the spectrum of sleep-wake disorders that occur in childhood.

In the Ethical and Medicolegal Issues section, Dr Michael Rubin discusses shared medical decision making between physician and patient using a case in which the use of opioid therapy is considered in a patient with restless legs syndrome. In the Practice Issues article, Drs Jon Tippin and Mark Eric Dyken review the issues we need to be aware of regarding driving safety and fitness to drive in sleep disorders. In the Coding article, Dr Waleed Hamed El-Feky and Mr David A. Evans update us on sleep medicine coding and coverage guidelines.

As with every issue of *Continuum*, several opportunities exist for CME. After reading the issue and taking the Postreading Self-Assessment and CME Test written by Drs Ronnie Bergen and James W. M. Owens Jr, you may earn up to 12 *AMA PRA Category 1 Credits*<sup>TM</sup> toward self-assessment and CME. The Patient Management

Problem, written by Dr St. Louis, describes the case of a 62-year-old woman presenting with daytime tiredness. By following her case and answering 12 multiple-choice questions corresponding to diagnostic and management decision points along the course of her disorder, you will have the opportunity to earn up to 2 *AMA PRA Category 1 CME Credits*. Canadian participants can now claim a maximum of 14 hours toward the Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Office of Continuing Medical Education and Professional Development, University of Calgary, for completing the Postreading Self-Assessment and CME Test and the Patient Management Problem.

My sincere gratitude to Dr St Louis for his expert leadership as well as his attentiveness and responsiveness in the creation of this issue (and his devotion as a member of the *Continuum* Editorial Board, as well). I would like to extend a similar thank you to the expert authors who have so thoughtfully and carefully lent their substantial knowledge to “talk us” through our care of the many patients presenting primarily because of disordered sleep or whose neurologic disorders impact, or are impacted by, the quality of their sleep.

—Steven L. Lewis, MD, FAAN  
Editor-in-Chief

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# Brain Circuitry Controlling Sleep and Wakefulness

Richard L. Horner, PhD; John H. Peever, PhD

## ABSTRACT

**Purpose of Review:** This article outlines the fundamental brain mechanisms that control sleep-wake patterns and reviews how pathologic changes in these control mechanisms contribute to common sleep disorders.

**Recent Findings:** Discrete but interconnected clusters of cells located within the brainstem and hypothalamus comprise the circuits that generate wakefulness, non-rapid eye movement (non-REM) sleep, and REM sleep. These clusters of cells use specific neurotransmitters, or collections of neurotransmitters, to inhibit or excite their respective sleep- and wake-promoting target sites. These excitatory and inhibitory connections modulate not only the presence of wakefulness or sleep, but also the levels of arousal within those states, including the depth of sleep, degree of vigilance, and motor activity. Dysfunction or degeneration of wake- and sleep-promoting circuits is associated with narcolepsy, REM sleep behavior disorder, and age-related sleep disturbances.

**Summary:** Research has made significant headway in identifying the brain circuits that control wakefulness, non-REM, and REM sleep and has led to a deeper understanding of common sleep disorders and disturbances.

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Dr Horner has received personal compensation for serving as a consultant for Dairy Farmers of Canada and Viord Inc and receives royalties from BookBaby for his book, *The Universal Pastime: Sleep and Rest Explained*. Dr Horner has received grants from Canada Research Chair (950-229813), the Canadian Institutes of Health Research (MT-15563), and the National Sanitarium Association Innovative Research Program (00144051). Dr Peever has received grant support from the Canadian Institutes of Health Research.

## Unlabeled Use of

## Products/Investigational Use Disclosure:

Drs Horner and Peever report no disclosures.

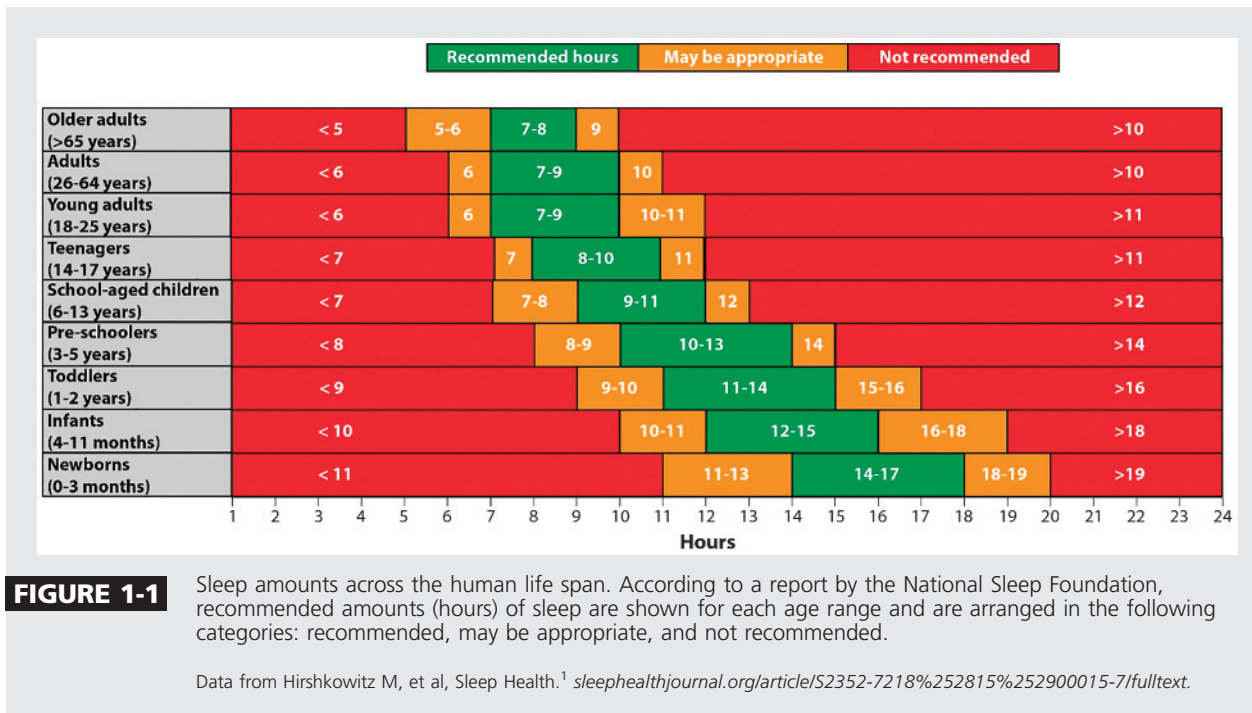
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## INTRODUCTION

From birth until death, the human brain spends one or more periods of each 24-hour day in wakefulness and the remaining hours in sleep. Different people sleep different amounts (typically 7 to 9 hours per day) to equip them with optimal alertness, attention, performance, and executive function. **Figure 1-1** summarizes the recommendations for sleep time durations across the life span based on an extensive literature review by a panel of scientists and clinicians.<sup>1</sup> The physiologic and neurobiological mechanisms that influence the timing of sleep onset and offset are introduced in this article.

Sleep duration is one of the two major components underlying optimal

sleep, the other being sleep intensity. Sleep intensity, or depth, is commonly measured as the difficulty in waking someone up from sleep in response to a given stimulus, such as an auditory tone. Such an index of sleep depth is correlated with the prominence of high-voltage slow waves in the EEG. Based on the distribution of sleep stages throughout the night, normal sleep is typically characterized by: (1) deep non-rapid eye movement (non-REM) sleep predominating at the beginning of the night, (2) lighter non-REM sleep and increasing intrusions of wakefulness toward the end of the night, and (3) increasing REM sleep amounts and intensity throughout the night. The brain mechanisms that generate these states of



#### KEY POINTS

- Different people sleep different amounts, but normal healthy adults generally sleep between 7 and 9 hours per day. However, daily sleep times vary among people and across their life spans.
- Cell groups located primarily in the brainstem and hypothalamus function to drive the individual behavioral states of sleep and wakefulness. These cell groups are mutually connected and use specific neurotransmitters to promote each brain state by either inhibiting or activating their respective target sites.

wakefulness, non-REM, and REM sleep are the major focus of this article, which serves as a key to understanding where the breakdown or pathophysiologic changes occur in the different sleep disorders.

#### BRAIN MECHANISMS OF WAKEFULNESS AND SLEEP

Several discrete clusters of cells exist in distinct regions of the brain that together comprise the interconnected circuits generating the states we recognize as wakefulness, non-REM sleep, and REM sleep. These interconnecting clusters of brain cells use individual neurotransmitters, or collections of neurotransmitters, to inhibit or excite their target sites. These excitatory and inhibitory connections modulate not only the presence of wakefulness or sleep per se, but also the levels of arousal within those states, including the depth of sleep, degree of vigilance, and motor activity. Some commonly used drugs modulate these excitatory and inhibitory connections and thus exert alerting or sedating properties or

influence specific components of sleep behavior. Examples of such drugs and their mode of action on aspects of the sleep-wake circuitry will be discussed in appropriate sections of this review.

Individuals experience what would be classified as normal sleep behavior when the activity of these cell clusters and circuits change in a normally coordinated sequence in time and place within the brain. However, sleep disorders are common and varied.<sup>2,3</sup> Suboptimal timing or quality of sleep can occur as a result of two major factors that are not mutually exclusive: (1) a primary sleep disorder (eg, insomnia, narcolepsy, restless legs syndrome, sleep-related breathing problems, and circadian rhythm sleep-wake disorders) or (2) lifestyle influences (eg, phase shifts due to occupational or recreational activities such as shift work, lack of exposure to direct sunlight, or extended nocturnal exposure to artificial light).

Each of these sleep disorders is introduced and explained in subsequent articles in this issue. However, two

important overarching principles are outlined in this introductory discussion on sleep neurobiology and physiology that relate to sleep disorders:

1. *Sleep is best optimized when the sleep period is appropriately aligned with an individual's circadian body clock (ie, when the sleep type is aligned with chronotype).* Misalignment or mismanagement of this optimal relationship can result in experiences of poor sleep quality, inappropriate sleepiness, and sleep initiation or maintenance insomnia. Such misalignment occurs in shift work sleep disorder, advanced or delayed sleep-wake phase disorders, and irregular sleep-wake phase disorder.<sup>2</sup>
2. *Sleep parasomnias are best explained by the basic premise that sleep and wakefulness are not mutually exclusive states and can dissociate.* Such dissociation can result in components of behaviors that are normally associated with wakefulness temporarily overlapping with sleep.<sup>4,5</sup> Such overlap causes a class of sleep disorders that are classified as the parasomnias and defined as behaviors or experiences intruding into sleep.<sup>2,6</sup> This overlap of waking and sleep behaviors/experiences produces identifiable and discrete clinical parasomnias (eg, REM sleep behavior disorder [RBD], hypnagogic hallucinations, sleep paralysis, somnambulism, somniloquy, sleep terrors, and bruxism).<sup>2</sup>

Overall, understanding how normal sleep-wake behavior is generated is a prerequisite to understanding the pathophysiology underlying the spectrum of clinical sleep disorders. Ac-

cordingly, this article first introduces the brain mechanisms that generate the states of wakefulness and sleep. The article then focuses on sleep disorders (narcolepsy and RBD) to highlight how current research findings are identifying the pathophysiologic underpinnings of the mechanisms and management of such disorders.

### Wakefulness-Generating Circuits

Several neuronal groups contribute to the brain activation of wakefulness, which is characterized by low-voltage and fast-wave EEG activity and resting postural motor tone in the EMG. Lesions or degeneration of the ascending projections of the arousal circuits can produce excessive sleepiness and are thought to underlie the outbreak of encephalitis lethargica in the 1920s.<sup>7,8</sup> Drug-induced modulation of these circuits facilitates sedation and sleep.

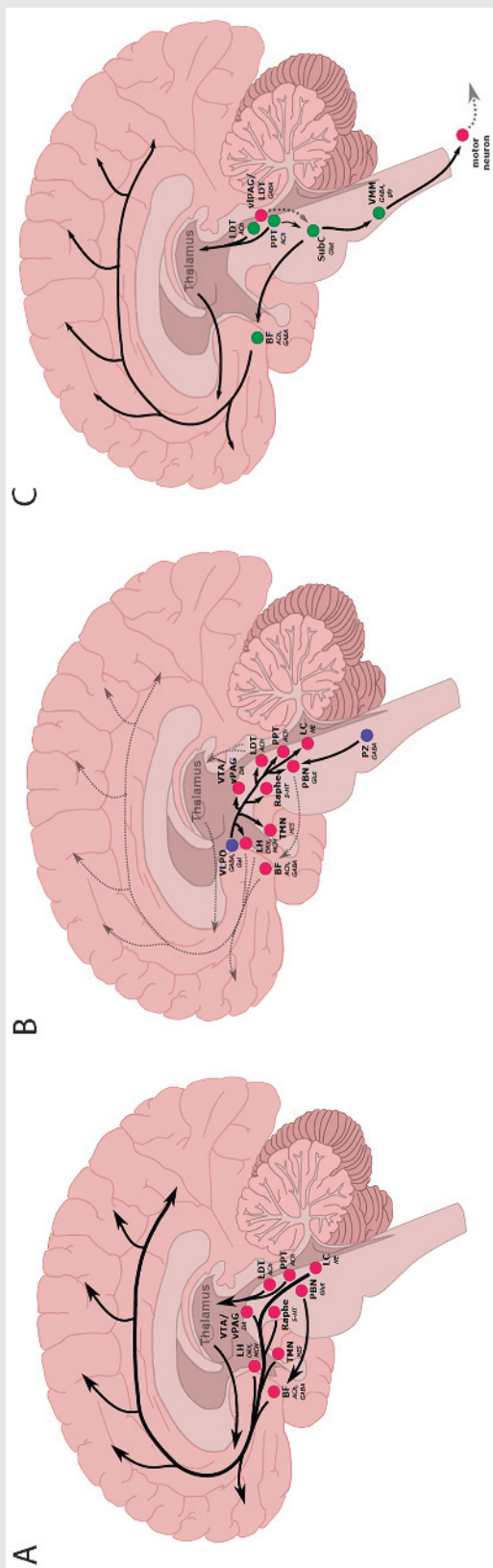
Of significance to the initial discussion of wakefulness-generating systems are the neuronal groups containing norepinephrine, histamine, serotonin, and dopamine (**Figure 1-2A**). Because of commonalities in the chemical structure of these neuromodulators, they are collectively grouped under the term *monoamines*. Other cell groups also contribute to the activated brain state of wakefulness. Accordingly, orexin (hypocretin), acetylcholine, and glutamate-containing cell groups are also introduced in this section.

Norepinephrine-containing neurons of the locus coeruleus in the dorsal pons have widespread projections throughout the brain, including the forebrain and cerebral cortex, in addition to brainstem arousal and autonomic systems (**Figure 1-2A**). Their activation contributes to attention, cortical arousal, as well as autonomic activation to support these processes. Correspondingly, the activity of locus

#### KEY POINTS

- Sleep is optimized when the sleep period is aligned with an individual's circadian body clock.
- Diffuse circuits located in the brainstem, hypothalamus, and basal forebrain contain glutamate, norepinephrine, histamine, serotonin, dopamine, and orexin, which serve to promote wakefulness.




**FIGURE 1-2**

Hypothesized circuits underlying wakefulness, non-rapid eye movement (non-REM) sleep, and REM sleep. **A**, Diffuse circuits located throughout the brainstem, hypothalamus, and basal forebrain promote wakefulness. Wakefulness-promoting cells located in the parabrachial nucleus (PBN; glutamate), locus coeruleus (LC; norepinephrine), laterodorsal tegmental nuclei (LDT), pedunculopontine tegmental nuclei (PPT; acetylcholine), tuberomammillary nucleus (TMN; histamine), dorsal raphe nucleus (serotonin), ventral tegmental area and periaqueductal gray (VTA/VPAG; dopamine), and lateral hypothalamus (LH; orexin [ORX]); melanin-concentrating hormone [MCH]) project to the thalamus, basal forebrain (BF), or cortex to support arousal. **B**,  $\gamma$ -Aminobutyric acid (GABA) and VLPO neurons induce non-REM sleep by projecting to and inhibiting the cell circuits that promote wakefulness (**A**). GABA cells in the PZ also promote non-REM sleep by inhibiting wakefulness-promoting neurons in the parabrachial nucleus. **C**, Circuits that promote REM sleep and REM sleep paralysis are located in the brainstem. Glutamate cells in the subcoeruleus nucleus (SubC) project to and excite GABA and glycine (Gly) cells in the ventromedial medulla (VMM), which, in turn, project to somatic motor neurons to cause REM sleep paralysis (atonia). These same cells also participate in controlling the timing of REM sleep itself. They do this, in part, by projecting to the basal forebrain, which causes the cortical activation that defines the brain arousal state during REM sleep. Cholinergic cells in the PPT and LDT also communicate with the SubC to impact REM sleep timing and control. Importantly, REM sleep is suppressed by GABA cells in the ventrolateral periaqueductal gray (VLPO) that project to and inhibit the glutamate cells in the SubC that promote REM sleep.

Ach = acetylcholine; DA = dopamine; GABA =  $\gamma$ -aminobutyric acid; Glut = glutamate; HIS = histamine; NE = norepinephrine; 5-HT = 5-hydroxytryptamine.

coeruleus neurons is maximal in wakefulness, declines in non-REM sleep, and is minimal in REM sleep. Stimulant medications (eg, methylphenidate, amphetamines) facilitate noradrenergic projections to promote alertness in patients with hypersomnia disorders.

Histamine-containing neurons in the tuberomammillary nucleus of the caudal hypothalamus contribute to brain arousal via excitatory projections to the basal forebrain, cerebral cortex, and brainstem. The tuberomammillary nucleus is the one major source of brain histamine and has widespread projections throughout the central nervous system (**Figure 1-2A**). The activity of histaminergic neurons is maximal in wakefulness, declines in non-REM sleep, and is minimal in REM sleep. Through this organization and activity profile, antihistamines that penetrate the blood-brain barrier promote drowsiness and sleep.

Two major collections of serotonin-containing neurons exist: (1) rostral groups in the pons known as the dorsal raphe nuclei, and (2) caudal groups in the medulla known as the caudal raphe nuclei. The pontine dorsal raphe serotonergic neurons project to the cortex and contribute to brain arousal (**Figure 1-2A**), whereas the medullary caudal raphe group primarily projects to the brainstem and spinal cord and facilitates autonomic and motor functions to support waking activities. Correspondingly, the activity of serotonergic neurons is maximal in wakefulness, declines in non-REM sleep, and is minimal in REM sleep.

Dopamine-containing neurons of the ventral tegmental areas and periaqueductal gray project to the striatum and frontal cortex. Activation of these dopamine-containing neurons is relevant to arousal and movement, but recordings from these neurons show that their activity profile is unlike the other monoaminergic

neurons (ie, wakefulness greater than non-REM sleep, with minimal activity in REM sleep for noradrenergic, histaminergic, and serotonergic neurons). The activity of dopaminergic neurons has not been as well documented as noradrenergic and serotonin systems, but recent photometry studies indicate that dopamine cells in the ventral tegmental area are most active in wakefulness and REM sleep and are least active during non-REM sleep. Activation of these neurons promotes wakefulness, whereas their inactivation promotes sleep.<sup>9</sup>

Orexin-containing neurons located in the lateral hypothalamus also have widespread projections to the brainstem, thalamus, hypothalamus, and cerebral cortex. The strongest projections are to the locus coeruleus. The activity of orexinergic neurons is maximal in periods of wakefulness associated with overt movements and motor activation and declines to minimal levels in non-REM sleep and REM sleep without muscle twitches (ie, periods identified as tonic REM sleep). Loss of orexin (hypocretin) neurons is involved in the clinical signs and symptoms of narcolepsy and cataplexy. Although modafinil is a widely prescribed stimulant and is prescribed for patients with narcolepsy, its mode of action is not well understood. Studies in preclinical animal models, however, have shown that modafinil increases immediate early gene (c-Fos) expression in orexin (hypocretin) cells indicative of neuronal activation and increases dopamine levels.

The two major collections of acetylcholine-containing neurons are (1) a basal forebrain group, and (2) two pontine groups, which include the laterodorsal tegmental and pedunculopontine tegmental nuclei (**Figure 1-2A**). The basal forebrain cholinergic group projects to the cortex and promotes cortical arousal and attentive states,

**KEY POINT**

■ The switch from wakefulness into non-rapid eye movement sleep is facilitated and maintained by a group of neurons that inhibit arousal-promoting circuits.  $\gamma$ -Aminobutyric acid-containing cell groups located in the ventrolateral preoptic area and medullary parafacial zone function to promote and stabilize non-rapid eye movement sleep.

whereas the pontine groups project to the thalamus and also facilitate cortical arousal. Importantly, two subpopulations of pontine cholinergic neurons are identifiable from their activity profiles. One group of cells has maximal activity in both wakefulness and REM sleep, facilitating low-voltage and fast-wave EEG activity common to both states. The second group has minimal activity in both wakefulness and non-REM sleep and has maximal activity in REM sleep that is largely responsible for the activated brain state of REM sleep; the contribution of the monoaminergic and orexinergic neurons to the EEG activation of REM sleep is minimal, as those neuronal groups are effectively silent in REM sleep.

The excitatory amino acid glutamate is present in neuronal groups throughout the pons and midbrain reticular formation. Glutamate is also present as a cotransmitter in most of the neuronal groups projecting to the brainstem, thalamus, hypothalamus, and cerebral cortex. The activity of the pontine and midbrain reticular neurons is typically maximal in wakefulness and minimal in non-REM sleep, with similar (or increased) levels in REM sleep. Recently, glutamatergic neurons in the parabrachial nucleus have been shown to significantly contribute to behavioral responsiveness and activated cortical activity via a relay involving the basal forebrain and lateral hypothalamus (Figure 1-2A).<sup>10,11</sup>

### **Non-Rapid Eye Movement Sleep-Generating Circuits**

Non-REM sleep is facilitated and maintained by a group of neurons that inhibit the brain-arousal systems of wakefulness (Figure 1-2B). The major non-REM sleep-generating cell groups are located in the ventrolateral preoptic area, anterior region of the hypothalamus, and the basal forebrain and have activity levels that are maximal in

non-REM sleep and lowest in wakefulness, with maintained (or modestly reduced) activity in REM sleep. These sleep-active cell groups synthesize and secrete the inhibitory amino acid  $\gamma$ -aminobutyric acid (GABA) and the neuropeptide galanin (Figure 1-2B). Overall, the high-voltage and slow-wave EEG activity that occurs in non-REM sleep is generated by a combination of two factors: (1) inhibition of the ascending brain arousal systems by the descending projections of these sleep-active GABA and galanin-containing inhibitory neurons and (2) activation of cortically projecting inhibitory neurons.

Importantly, these inhibitory sleep-active  $\gamma$ -aminobutyric acid-mediated (GABA-ergic) cell groups receive inhibitory inputs from neurons of the ascending arousal system. Through this organization, they are minimally active in wakefulness and states of heightened arousal. Likewise, these inhibitory GABA-ergic sleep-active cell groups project to, and inhibit, all the neuronal groups involved in arousal. The inhibitory non-REM sleep-generating system initiates and sustains sleep and inhibits arousal once these cell groups are released from inhibition and become active at sleep onset. This arrangement of reciprocal inhibition between arousal and non-REM sleep-generating neuronal systems has been termed the *sleep-wake switch*.<sup>8,12</sup>

However, the control of non-REM sleep also appears to be modulated by circuits in the brainstem. Using optogenetic and chemogenetic methods, Anacleit and colleagues<sup>13</sup> showed that direct activation of GABA-ergic neurons in the medullary parafacial zone can rapidly induce non-REM sleep (Figure 1-2B). Parafacial zone neurons monosynaptically innervate and release GABA onto parabrachial neurons, which, in turn, project to and

release glutamate onto magnocellular basal forebrain neurons. In addition to GABA/galanin ventrolateral preoptic cells, GABA-ergic parafacial zone neurons also appear able to trigger non-REM and slow-wave activity.

## Organization of the Sleep-Wake Switch

The arrangement of reciprocal inhibition between the arousal and non-REM sleep-generating circuits results in sustained periods of sleep and wakefulness that are coordinated and consolidated to appropriate periods across the day. In short, the arousal neurons reinforce their own activation by inhibiting sleep neurons, thus facilitating consolidated periods of wakefulness appropriate for optimal behaviors and cognition. Likewise, sleep-active GABA neurons reinforce their own activation by inhibiting arousal neurons, thus facilitating consolidated periods of sleep appropriate for optimal behavior and cognition in subsequent wakefulness.

This mutually inhibitory organization of the sleep-wake switch also provides a degree of resistance to changes in the sleep-wake state when one side of the switch is active. This steadiness and resistance to change when one side of the switch is active thus provides for consolidated periods of sleep at night and wakefulness during the day (ie, the sleep-wake switch is stable in either position). Neurodegeneration or lesions impacting some components of the sleep-wake switch can destabilize it. For example, loss of orexin (hypocretin) neurons in patients with narcolepsy reduces excitation of the arousal neurons, particularly of the locus coeruleus, which receives the densest innervation. This effectively unbalances the sleep-wake switch by both reducing levels of arousal, as well as removing inhibition

of the sleep-active GABA-ergic neurons, thus promoting sleepiness as well as fragmentation of wakefulness and sleep in patients with narcolepsy.

**Coordinating influence of the circadian timing system.** A question that arises concerning the sleep-wake switch is what causes the change in balance and a sudden switch in brain state at night and in the morning? The answer relates to the first overarching principle of sleep-wake physiology: Sleep is best optimized when the sleep period is appropriately aligned with an individual's circadian body clock.

In an average adult, a decline in body temperature at night (usually around 10:00 PM to 11:00 PM) precipitates optimal and typical sleep onset, with most individuals reporting that they find it difficult to fall asleep earlier than this time frame, and that it is harder to stay awake after this time. Likewise, a rise in body temperature in the morning (around 6:00 AM to 7:00 AM) in an average individual triggers normal awakening and alertness, with individuals commonly reporting that they find it difficult to wake up earlier than this time and to stay asleep after this time. Other individuals who are early birds or night owls, or patients diagnosed with advanced or delayed sleep-wake phase disorder, have either advanced or delayed sleep onset and offset times, as their circadian body temperature cycles are further advanced or delayed compared to that of the average person.

A major reason that self-selected sleep phase is strongly linked to the body temperature cycle is because body temperature has significant effects on the position of the sleep-wake switch. The circadian-mediated *decline* in body temperature at night activates sleep-active GABA neurons, thus promoting sleep via a change in position of the sleep-wake switch.



**KEY POINT**

■ Commonly used drugs can flip the sleep-wake switch toward alertness or sedation. For example, drugs that bind to  $\gamma$ -aminobutyric acid A receptors promote neuronal inhibition and sleepiness, whereas caffeine promotes wakefulness by antagonizing adenosine receptors that suppress sleep induction circuitry.

This body temperature-mediated activation of sleep-active GABA neurons also leads to inhibition of the arousal circuits via the reciprocal inhibition, resulting from the organization of the sleep-wake switch. The decline in body temperature at night therefore promotes sleep initiation and maintenance by tipping the balance of the sleep-wake switch simultaneously both away from arousal and toward sleep. Likewise, the circadian-mediated rise in body temperature in the morning inhibits sleep-active GABA neurons, thus promoting wakefulness via a reversal of the position of the sleep-wake switch, and also leads to activation of the arousal circuits. The rise in body temperature in the morning therefore promotes the normal initiation of awakening by tipping the balance of the sleep-wake switch simultaneously both toward arousal and away from sleep.

Self-selected sleep phase and optimal timing of sleep are strongly linked to the circadian body temperature cycle. The relationship of optimal sleep phase to the body temperature cycle persists, regardless of an individual's chronotype (ie, whether their chronotype fits with being an early bird or a night owl, having an average bedtime and waking schedule, or having advanced or delayed sleep-wake phase disorders). In each case, sleep onset is facilitated when an individual's body temperature declines because of their circadian rhythm, regardless of actual time of day, and, likewise, arousal is facilitated because of the circadian-mediated rise in body temperature, again regardless of actual time of day. For example, despite a night of shift work, people often report difficulty initiating and sustaining sleep the next day because the circadian variations in body temperature are not fully adjusted to the schedule (ie, similar to jet lag).

In summary, when sleep phase is appropriately aligned with an individual's body clock, then sleep timing, duration, and consolidation are all optimized. In contrast, when the sleep phase is inappropriately aligned with an individual's body clock, then sleep timing, duration, and consolidation are suboptimal. Under such conditions, sleep initiation or maintenance insomnia and sleep fragmentation are typically reported.

**Effects of drugs on the sleep-wake switch.** Commonly used drugs can also flip the sleep-wake switch toward alertness or sedation. For example, a variety of drugs bind to the GABA-A receptor and enhance the effects of GABA, thereby promoting neuronal inhibition and sleepiness. Such drugs include the benzodiazepines, imidazopyridines (ie, the nonbenzodiazepine sedative hypnotics), barbiturates, some IV and inhalational anesthetics (eg, propofol and isoflurane), and ethanol. Because of the anatomic arrangement of reciprocal inhibition between the arousal and sleep-generating circuits in the sleep-wake switch, all of these GABAergic agents effectively flip the switch toward sedation and, at the same time, away from arousal. However, because of widespread inhibitory influences of GABA-A receptor stimulation also contained within the respiratory network, an attendant risk exists of respiratory depression, hypoventilation, and asphyxia following administration of GABA-mimetic drugs, as well as a lack of compensatory respiratory and arousal responses to that depression.<sup>14</sup> Development of antagonists for the orexin (hypocretin) peptides also offers a promising avenue for drug development for insomnia, as well as providing for brain sedation with reduced risk of respiratory depression due to the lack of direct effects of the orexinergic antagonists on the GABAergic system.<sup>15</sup>

Caffeine is also widely used as a stimulant and acts as an adenosine receptor antagonist. Adenosine is released from neurons and glia, and adenosine levels increase as a function of cellular metabolism and rise during the day. Adenosine inhibits wake-active neuronal groups, and blockade of this inhibition with caffeine promotes brain arousal and effectively tips the sleep-wake switch toward arousal. Other central nervous system stimulants include amphetamines and cocaine, and these increase the synaptic concentrations of monoamines by blocking reuptake and increasing exocytosis. Administration of these drugs further tips the sleep-wake switch toward heightened arousal.

Melatonin is a commonly used over-the-counter sleep aid, but this drug may not exert direct influence on the sleep-wake circuitry. Instead, melatonin is a marker of, and is strongly aligned to, the circadian timing system. The appropriately timed administration of melatonin can be used to phase shift the circadian timing system<sup>16</sup> and, by so doing, can entrain circadian rhythms.<sup>15</sup> This effect of melatonin can explain improved sleep observed in individuals with disrupted circadian rhythms.<sup>15</sup>

**Effects of physiologic stressors on the sleep-wake switch.** Sleep-related breathing disorders are common and lead to recurrent episodes of asphyxia and sleep disturbance. The hypercapnic and hypoxic stimuli lead to activation of respiratory neurons in an attempt to increase lung ventilation and correct the asphyxia, and these stimuli also lead to activation of brainstem arousal neurons to trigger arousal from sleep.<sup>14</sup> Noradrenergic locus coeruleus neurons and serotonergic raphe neurons have been strongly implicated in these responses.<sup>17,18</sup> Developmental abnormalities in the integrated respiratory

and arousal responses to acute respiratory distress can predispose infants to increased risk of life-threatening events at night and sudden infant death syndrome.<sup>19</sup> Repeated exposure to intermittent hypoxia can also cause degeneration of noradrenergic locus coeruleus neurons, thus predisposing individuals to the risks of deteriorating respiratory and arousal responses to asphyxia and of respiratory failure.<sup>20</sup>

### **Rapid Eye Movement Sleep-Generating Circuits**

REM sleep is a state accompanied by dreaming, heightened brain neural activity, paralysis of the skeletal musculature (although the diaphragm is spared this inhibition), heightened respiratory and cardiovascular variability, and depressed respiratory responses to hypoxia and hypercapnia.<sup>14,21</sup> Disorders in discrete components of the REM sleep circuitry can lead to distinct clinical motor disorders and parasomnias.<sup>22,23</sup> REM sleep is present in homeotherms (ie, mammals and birds), but some mammals (eg, the permanently aquatic cetaceans such as whales and dolphins) have no identifiable REM sleep to no apparent detriment. The understanding of circuits generating REM sleep, which has undergone major revisions in recent years, is introduced below before discussion of associated clinical problems.

Two major circuits are involved in REM sleep generation, and their essential elements include interactions between (1) GABA and glutamatergic neurons and (2) monoaminergic and cholinergic neurons (**Figure 1-2C**).<sup>24</sup> The critical REM sleep-generating region is located in the dorsal pons, and activation of this region produces the defining signs of REM sleep, including low-voltage and fast-wave EEG activity and muscle atonia due to active suppression of postural motor tone.

# KEY POINTS

- Rapid eye movement sleep and its cardinal features (ie, cortical activation and muscle atonia) are generated by  $\gamma$ -aminobutyric acid, glutamate, and cholinergic neurons located in the brainstem.
- Identification of the brain circuits that control wakefulness and sleep has led to a deeper understanding of several sleep disorders.
- Narcolepsy is caused by loss of hypothalamic orexin cells and is characterized by excessive sleepiness, disturbed rapid eye movement sleep, sleep paralysis (atonia), and hypnagogic hallucinations.

In the GABA and glutamatergic mechanism of REM sleep generation, activation of pontine glutamatergic neurons of the subcoeruleus nucleus (also known as the sublateralodorsal tegmental nucleus) leads to REM sleep. These glutamatergic cells become active to generate REM sleep when they are released from inhibition by pontine GABA-ergic neurons located in the ventrolateral periaqueductal gray and lateral pontine tegmentum (**Figure 1-2C**).<sup>25,26</sup>

In the monoaminergic and cholinergic explanation of REM sleep generation, decreased activity of the monoaminergic cell groups preceding and during REM sleep withdraws inhibition of pontine cholinergic neurons. This withdrawal leads to increased acetylcholine release into the pontine reticular formation that promotes entry into REM sleep.<sup>27,28</sup>

The core circuit necessary for generating REM sleep involves the GABA-glutamate circuit.<sup>22,24</sup> Cholinergic activity arising from interactions within the monoaminergic-cholinergic circuit appears to serve an accessory role in REM sleep generation, reinforcing transitions into REM sleep from non-REM sleep.<sup>24</sup> Resolution of this REM sleep-generating circuitry and the primacy of one mechanism over another is an active area of research.<sup>24,28</sup> A recent study also identified GABA cells in the medial medulla as potential players in REM sleep modulation.<sup>29</sup>

Spinal motor activity in REM sleep is suppressed through recruitment of descending neural circuits that involve glycine (principally) and GABA (**Figure 1-2C**). Disruption of this descending spinal motor inhibitory pathway can lead to RBD. Suppression of motor activity in the muscles surrounding the upper airway during physiologic atonia in REM sleep can lead to periods of upper airway narrowing and collapse, resulting in

snoring, hypoventilation, and obstructive sleep apnea. However, the periods of major suppression of upper airway muscle activity that occur in REM sleep do not seem to involve the same mechanism as for the suppression of spinal motor activity. For example, the tongue musculature is suppressed through two additional processes in REM sleep: first, with withdrawal of excitation (ie, a process of disfacilitation) mediated principally by reduced monoaminergic and glutamatergic inputs to the hypoglossal motor pool, and, second, with recruitment of REM sleep inhibition mediated by a muscarinic receptor mechanism linked to a G protein-coupled inwardly rectifying potassium channel.

## DYSFUNCTION OF SLEEP-WAKE CIRCUITRY UNDERLIES SLEEP DISORDERS

Investigation of the fundamental brain mechanisms underlying sleep-wake control has laid the foundation for understanding the pathophysiology of several sleep disorders. Breakdown in sleep-wake circuits and the communication between them contributes to both narcolepsy and REM sleep behavior disorder. Changes in the circuits controlling non-REM sleep lead to degeneration of normal sleep-wake patterns that occur with age and in Alzheimer disease.

### Narcolepsy

Narcolepsy is a debilitating sleep disorder that can impair a person's ability to work, socialize, and drive safely. Narcolepsy is caused by loss of hypothalamic orexin cells and is characterized by excessive sleepiness, disturbed REM sleep, sleep paralysis (atonia), and hypnagogic and hypnopompic hallucinations. Another common symptom of narcolepsy is cataplexy, which is the involuntary onset of skeletal muscle

paralysis or weakness during otherwise normal wakefulness; these attacks are debilitating for patients because they leave the affected individual conscious but unable to move and create risk for falls and injury. The neural mechanisms that trigger cataplexy are unclear, but it is hypothesized that it results from intrusion of normal REM sleep paralysis into wakefulness (Case 1-1).

Our understanding of the mechanisms of REM sleep is helping to identify some of the potential causes of cataplexy. Converging lines of evidence suggest that cataplexy and REM sleep share a common neural mechanism. For example, tricyclic antidepressants, which are used to alleviate cataplexy, also suppress REM sleep, and rapid withdrawal of these drugs causes large rebounds in both cata-

plexy and REM sleep.<sup>30-32</sup> Muscle stretch and monosynaptic H reflexes are absent during both cataplexy and REM sleep.<sup>33,34</sup> Neuroimaging studies in patients with narcolepsy and electrophysiologic recordings from isolated neurons in narcoleptic dogs show that the brainstem circuitry involved in REM sleep has similar activity during both REM sleep and cataplexy.<sup>35-38</sup> For example, in narcoleptic dogs, cells in the locus coeruleus (a brainstem region involved in REM sleep control) abruptly cease firing during both REM sleep and cataplexy,<sup>39</sup> and cells in the medullary gigantocellular nucleus (a region critical for promoting REM sleep paralysis) increase their activity during both REM sleep and cataplexy.<sup>40</sup> In addition, serotonin cells in the dorsal raphe nucleus, which are associated

#### KEY POINT

■ Cataplexy may be caused by inappropriate recruitment of circuits that generate rapid eye movement sleep paralysis.

## Case 1-1

A 17-year-old boy, who had been highly motivated and had excellent grades in school, suddenly began experiencing relentless sleepiness. No matter how much he slept, he continued to struggle to stay awake during the day, although he felt refreshed immediately after awaking in the morning or after a daytime nap. He also reported that his sleep was restless, and he often experienced frequent nighttime awakenings. His persistent daytime sleepiness and lack of vigilance began to impact his ability to study for school, and his grades declined. He also reported that he would awaken from vivid dreams but was unable to move for several seconds afterward despite being awake and conscious. He also reported apparent vivid, dreamlike hallucinations while dozing off to sleep on several occasions. About a month after developing sleepiness, he experienced two episodes of bilateral muscle weakness that caused him to suddenly slump down in his chair despite remaining fully conscious. These attacks lasted about a minute each and occurred while he was laughing heartily.

**Comment.** This is a typical account of narcolepsy. Many patients are diagnosed in their teenage years, often after developing sleepiness and restless nighttime sleep. Sleepiness persists despite increasing amounts of nighttime sleep or after adding daytime naps to their sleep schedules. Daytime sleepiness typically has a major impact on their daytime functioning. Sleep paralysis (inability to move after waking from a dream) and hypnagogic hallucinations (vivid dreamlike experiences while falling asleep) are also common symptoms in narcolepsy. However, the tell-tale sign of narcolepsy is cataplexy (the sudden onset of muscle weakness or paralysis following a very humorous or emotionally charged situation). Narcolepsy results from death of orexin (hypocretin) cells in the lateral hypothalamus.

**KEY POINTS**

- Cataplexy attacks are usually triggered by strong positive emotions such as excited laughter, elation, or surprise, but they are also associated with negative emotions such as fear.
- The amygdala regulates emotions and is activated during cataplexy; therefore, it may play a central role in triggering cataplexy attacks that occur in response to strong positive emotions.
- Rapid eye movement sleep behavior disorder is a parasomnia that is characterized by excessive and elaborate movements during rapid eye movement sleep.

with modulating behavioral arousal,<sup>41</sup> also influence cataplexy. Restoration of orexin receptors onto dorsal raphe neurons in mice that lack these receptors decreases cataplectic attacks in this model of narcolepsy.<sup>42</sup>

Some patients with narcolepsy report hypnagogic hallucinations during cataplectic attacks, and some patients enter REM sleep during cataplexy, suggesting that such attacks result from inappropriate recruitment of REM sleep circuits. Recent data show that cataplexylike attacks can be triggered in orexin knockout mice (ie, narcoleptic mice) by activating the brainstem circuit (ie, the subcoeruleus nucleus) that controls REM sleep.<sup>43</sup> This observation suggests that cataplexy may result from pathologic recruitment of the circuits that cause REM sleep paralysis, and that muscle paralysis in REM sleep and cataplexy stem from a common neural mechanism.

It is important to recognize that cataplexy attacks are usually triggered by strong positive emotions such as excited laughter, elation, or surprise, but they are also associated with negative emotions such as fear. The association between emotion and cataplexy suggests that circuits regulating emotion may also play a role in cataplexy control. The amygdala is a brain structure that not only underlies the processing of emotions, but is one that has been associated with REM sleep regulation<sup>44</sup> and could therefore be involved in controlling emotionally triggered cataplexy. The link between the amygdala and cataplexy is supported by imaging studies showing that the amygdala is activated during cataplexy.<sup>36</sup> In narcoleptic dogs, neurons of the amygdala increase firing during cataplectic attacks.<sup>35</sup> A recent study indicates that bilateral lesions of the amygdala significantly reduce the frequency of cataplectic attacks in mice

lacking orexin.<sup>45</sup> Furthermore, GABAergic neurons in the amygdala send descending projections to critical elements of sleep-wake circuitry, including the locus coeruleus, the lateral pontine tegmentum, the ventrolateral periaqueductal gray, as well as the subcoeruleus, which is a critical part of the REM sleep-generating circuit.<sup>45</sup>

However, one of the strongest associations between narcolepsy and the dysfunction of sleep-wake circuits arises from the fact that arousal-promoting orexin neurons are lost in human narcolepsy and that loss of orexin and orexin cells and mutation of orexin receptors can trigger symptoms of narcolepsy in dogs and mice, which could explain the profound sleepiness that defines narcolepsy.<sup>23</sup> This concept is supported by multiple lines of experimental data showing that orexin cells are most active during wakefulness, and that their direct activation or inactivation promotes arousal and sleep, respectively.<sup>46</sup> Another link between the orexin system and narcolepsy stems from the fact that orexin neurons are highly responsive to strong positive emotions; therefore, the loss of these neurons in patients with narcolepsy may destabilize the natural muscle regulation system within the brainstem and allow positive emotions to trigger motor paralysis.<sup>47,48</sup>

### **Rapid Eye Movement Sleep Behavior Disorder**

RBD is a parasomnia that is characterized by excessive and elaborate movements during REM sleep. Movements in RBD range from simple motor activity such as talking, shouting, and limb jerking, to more complex movements such as gesturing, punching, or kicking. Movements in RBD are often so violent that they cause injury to the patient or their bed partner and can cause severe injuries (eg, lacerations or



broken bones) that may require medical treatment. RBD is a serious health problem because most patients eventually develop a neurodegenerative disease that is characterized by  $\alpha$ -synuclein deposition.<sup>49</sup> RBD is currently the strongest predictor of the onset of neurodegenerative diseases, with more than 80% of patients developing Parkinson disease (PD), dementia with Lewy bodies, or multiple system atrophy. Therefore, identification of prodromal neurodegeneration before actual disease onset has major clinical implications. Scientifically, RBD presents a unique opportunity to study the development of a neurodegenerative syndrome from its prodromal stages and may be the ideal way to develop neuroprotective therapies for the prevention of ensuing degenerative disorders.<sup>50</sup>

The close association between RBD and the subsequent development of synucleinopathies suggests that RBD itself could result from a neurodegenerative process. One possibility is that RBD arises from neurodegeneration of the circuits that control healthy REM sleep, and subsequent pathologies develop as degeneration spreads rostrally. Although this idea remains speculative, it fits well with the classic model of PD pathogenesis by Braak and colleagues,<sup>51</sup> which proposes that neurodegeneration starts in the brainstem before ascending rostrally into the central nervous system structures associated with the classic motor and cognitive features of PD. Clinical data support this idea. For example, patients with RBD often exhibit PD-like symptoms (eg, bradykinesia) before they are clinically diagnosed with PD,<sup>52</sup> suggesting that RBD and PD symptoms stem from a common neurodegenerative process that potentially affects the caudal brainstem areas associated with REM sleep and movement.

Studies indicate that RBD could be caused by degeneration of the circuits that control healthy REM sleep (Figure 1-2C).<sup>53</sup> For example, experimentally induced lesions of the core REM sleep circuits, including the subcoeruleus nucleus and ventral medial medulla, cause RBD-like motor behaviors in cats, rats, and mice.<sup>54,55</sup> This observation is in line with clinical neuroimaging studies and postmortem tissue analysis showing damage or defects of the brainstem regions that house REM sleep circuits in patients with RBD.<sup>49,56,57</sup> However, and perhaps most importantly, recent studies show that some patients with RBD have Lewy bodies, neuronal loss, depigmentation, or gliosis within (or near) the circuits that control normal REM sleep (eg, subcoeruleus, ventral medial medulla, and pedunculopontine tegmental nucleus).<sup>49,58–64</sup> These findings not only support the neuroimaging findings of neuronal cell loss in these areas associated with RBD pathogenesis,<sup>56,57</sup> but they also substantiate basic neuroscience data showing that lesions within the REM sleep circuits trigger RBD-like behaviors in animals.<sup>65–68</sup> Therefore, one possibility is that RBD is caused by degeneration of the core circuits that control healthy REM sleep.

However, some forms of RBD probably do not stem from neurodegenerative processes. For example, RBD also can be triggered by brainstem tumors, infarcts, and lesions.<sup>69,70</sup> The location of these lesions is typically confined to brainstem regions associated with REM sleep control. RBD is also associated with alcohol withdrawal and is common in long-term antidepressant users.<sup>71</sup> RBD in these situations could stem from a drug-induced imbalance in the normal biochemical mechanisms that control REM sleep. Data suggest that RBD could also result from disturbances in the normal biochemical

#### KEY POINTS

- Rapid eye movement sleep behavior disorder is the strongest predictor of the onset of neurodegenerative diseases, with more than 80% of patients developing Parkinson disease, dementia with Lewy bodies, or multiple system atrophy.
- Degeneration of rapid eye movement sleep circuits in the brainstem underlies the motor symptoms of rapid eye movement sleep behavior disorder.

**KEY POINT**

■ Loss of non-rapid eye movement sleep-generating cells in the ventrolateral preoptic area is associated with sleep fragmentation during aging, and more severe loss of ventrolateral preoptic cells is associated with greater non-rapid eye movement sleep disturbance in patients with neurodegenerative disorders.

mechanisms that control REM sleep. For example, pharmacologic blockade of either GABA/glycine or cholinergic inhibition results in enhanced motor activity during REM sleep,<sup>54,72,73</sup> suggesting that imbalances in the release of these transmitters could facilitate RBD-like movements. In addition, overactivation of the red nucleus (a region that controls muscle twitches during REM sleep) triggers excessive movements during REM sleep in mice and rats. Together, these observations suggest that the exaggerated motor activity in patients with RBD can result from overexcitation of circuits generating twitches or breakdown of biochemical mechanisms that normally suppress motor activity in REM sleep.

Another line of evidence supporting the claim that RBD could stem from a biochemical imbalance in REM control mechanisms comes from a genetic study in mice.<sup>54</sup> This study showed that RBD-like behaviors can be triggered in transgenic mice with deficient glycine and GABA transmission, which are not only key players in promoting REM sleep paralysis, but are also important in controlling REM sleep timing. Brooks and Peever<sup>54</sup> found that impaired inhibitory transmission not only induced overt RBD-like motor behaviors (eg, chewing, face grooming, running), but it also caused mild sleep disturbances and cortical EEG slowing, which are both findings in RBD. However, Brooks and Peever<sup>54</sup> also found that RBD symptoms could be mitigated by treating mice with either clonazepam or melatonin (two effective treatments for RBD). These findings suggest that impairments or imbalances in central nervous system neurotransmission, particularly, in GABA and glycine transmission, could contribute to RBD pathogenesis.

If both RBD and narcolepsy arise from disturbances in REM sleep con-

trol, then a link should exist between these disorders. In fact, RBD is common in patients with narcolepsy. Approximately 45% to 61% of patients who have narcolepsy with cataplexy (narcolepsy type 1) experience RBD.<sup>74</sup> Interestingly, patients with narcolepsy with cataplexy are more frequently affected by RBD than those who have narcolepsy without cataplexy (narcolepsy type 2). Also, RBD can be triggered or aggravated by antidepressant treatment in patients with narcolepsy with cataplexy. In addition, many patients with narcolepsy exhibit marked increases in overall levels of motor activity during REM sleep, even if they do not experience frank RBD. Therefore, one major commonality between RBD and narcolepsy is abnormal motor activity, with RBD resulting from loss of normal REM sleep paralysis, and cataplexy resulting from intrusion of REM sleep paralysis into wakefulness. These clinical observations suggest that RBD and narcolepsy may result from abnormal control of the circuits that underlie REM sleep, and particularly those that regulate REM sleep paralysis.

### **Age-Related Sleep Disturbances**

Investigation of the brain mechanisms underlying non-REM sleep control has also improved our understanding of age-related changes in sleep. Disturbed sleep is a common and troubling symptom associated with both normal aging and certain degenerative disorders such as Alzheimer disease. Multiple lines of data suggest that GABA- and galanin-containing cells in the ventrolateral preoptic area play a role in controlling non-REM sleep<sup>8</sup> (Figure 1-2B). For example, targeted lesions of ventrolateral preoptic cells cause fragmented sleep in rodents, and optogenetic activation of ventrolateral preoptic cells induces non-REM

sleep in mice. Recently, Lim and colleagues<sup>75</sup> found that cell loss within the intermediate nucleus (the ventrolateral preoptic homologue in humans) was correlated with sleep fragmentation in elderly (approximately 89 years of age) individuals and those with Alzheimer disease.<sup>75</sup> Specifically, they found that individuals with more galanin-containing ventrolateral preoptic neurons had better sleep, whereas those with fewer ventrolateral preoptic neurons had more fragmented sleep patterns. This work suggests that the ventrolateral preoptic area in humans promotes non-REM sleep, and that degeneration or neuronal loss in this critical area is associated with age-related changes in normal sleep patterns in older adults, and that greater ventrolateral preoptic cell loss in neurodegenerative disorders may result in more deranged non-REM sleep architecture.

## CONCLUSION

Cell groups located primarily in the brainstem and hypothalamus function to drive the individual behavioral states of sleep and wakefulness. These cell groups are mutually connected and use specific neurotransmitters to promote each brain state by either inhibiting or activating their respective target sites. Diffuse circuits that contain glutamate, norepinephrine, histamine, serotonin, dopamine, and orexin promote wakefulness (**Figure 1-2A**). The switch from wakefulness into non-REM sleep is facilitated and maintained by a group of neurons that inhibit arousal-promoting circuits (**Figure 1-2B**). GABA-containing cell groups located in the ventrolateral preoptic area and medullary parafacial zone function to promote and stabilize non-REM sleep. REM sleep and its cardinal features (ie, cortical activation and muscle atonia) are primarily

generated by GABA, glutamate, and cholinergic neurons located in the brainstem (**Figure 1-2C**). However, it remains unclear how these brainstem circuits communicate with the cell groups that initiate wakefulness and non-REM sleep. Identification of the brain circuits that control wakefulness and sleep has led to a deeper understanding of several sleep disorders. Loss of orexin cells underlies the sleepiness of narcolepsy, and pathologic recruitment of REM sleep-promoting circuits is associated with cataplexy in narcolepsy. Degeneration of REM sleep circuits underlies motor symptoms in RBD, whereas loss of non-REM sleep-generating cells is associated with sleep fragmentation during aging and neurodegenerative disorders.

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# Diagnostic Approach and Investigation in Sleep Medicine

Michael H. Silber, MBChB, FAAN

## ABSTRACT

**Purpose of Review:** This article provides a clinical approach to the appropriate investigation and diagnosis of sleep disorders commonly seen by neurologists.

**Recent Findings:** Home sleep apnea testing in appropriate situations can replace laboratory polysomnography in many cases of uncomplicated sleep apnea. Multiple sleep latency tests must be performed meticulously and interpreted in the clinical setting to avoid overdiagnoses of narcolepsy. Human leukocyte antigen testing has limited utility in establishing a diagnosis of narcolepsy because a positive test has low specificity. Rapid eye movement (REM) sleep behavior disorder is frequently the first manifestation of an evolving synucleinopathy, and a careful history and neurologic examination are needed to determine other early features of these disorders.

**Summary:** A meticulous history from the patient, supplemented by collateral history from an observer, is essential to establishing the diagnosis of sleep disorders. Judicious supplementary use of investigations, such as laboratory polysomnography, home sleep apnea testing, wrist actigraphy, and multiple sleep latency tests, can confirm the correct diagnosis. This article describes an approach to the sleepy patient, the patient with neuromuscular disease and possible sleep-disordered breathing, the patient with restless legs syndrome, and young and older patients with abnormal movements during sleep.

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## INTRODUCTION

Sleep medicine, like most of neurology, relies on the taking of meticulous and accurate histories to reach diagnoses. Investigations serve as an extension of the clinical method and not as tests to be interpreted in isolation. Judgment and experience are required in deciding which patients require sleep studies, which study is most appropriate for a specific patient, and how to interpret the results of testing. The holistic management of patients is emphasized, with the numeric results of a sleep study providing only a subset of the information required to empower patients to make wise health decisions.

The basic sleep history incorporates an understanding of not only patients' nights, but also their days. More than in most areas of neurology, collateral history from bed partners, caregivers, or observers is essential to the understanding of the symptoms and their significance. **Table 2-1** lists the components of the sleep history. An overview of a night's sleep includes exploration of sleep initiation, continuity, and termination on weekdays and weekends. Specific nocturnal symptoms include breathing abnormalities at night and excessive movements during sleep. Daytime symptoms focus on sleepiness, work and leisure activities, and the presence or absence of



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# KEY POINT

■ Diagnoses in sleep medicine are dependent on careful and meticulous histories, which are aided by observers, and investigations should be seen as an extension of the classic clinical method, rather than independent diagnostic tools.

**TABLE 2-1** Components of the Sleep History

- **Overview of a Typical Night's Sleep**
  - Sleep initiation
  - Sleep maintenance
  - Sleep termination
  - Differences between work weeks, weekends, and vacations, and whether any shift work occurs
- **Specific Nocturnal Symptoms**
  - Respiration (eg, snoring, apneas)
  - Movements (eg, restless legs, periodic limb movements, parasomnias, seizures)
- **Daytime Symptoms**
  - Excessive daytime sleepiness
  - Cataplexy, hallucinations, sleep paralysis
- **Psychosocial, Medical, and Family History**
  - Occupation and family circumstances
  - Substance use
  - Exercise
  - Depression or anxiety

cataplexy. Psychosocial history is especially important in sleep medicine, including the use of alcohol, nicotine, and caffeine; exercise; and symptoms of depression and anxiety. Patient-completed sleep questionnaires and validated scales, such as the Epworth Sleepiness Scale, may provide useful additional information.

Specific investigations available for assessing patients with sleep problems include laboratory-based polysomnography, home sleep apnea tests, overnight oximetry, wrist actigraphy, and multiple sleep latency tests (MSLTs). For certain disorders, EEG, MRI scans of the head, urine drug

screens, neuropsychometric testing, relevant blood tests, pulmonary function tests, and others may add ancillary information.

This article takes a pragmatic approach based on the clinical problems likely to be encountered by a practicing neurologist. In each section, the salient features found on history, relevant physical examinations, and the appropriate investigations will be discussed.

## THE SLEEPY PATIENT

Excessive daytime sleepiness is one of the most common indications for a sleep medicine consultation. **Table 2-2** provides a practical classification of the causes of hypersomnolence and the assessment tools appropriate for each disorder. Voluntary sleep deprivation (insufficient sleep syndrome) is probably the most prevalent cause of excessive daytime sleepiness in North America, with multiple contributing factors, including both adult members of a family working outside the home, multiple jobs in a difficult economy, and the nightly use of electronic devices linked to the Internet. Hypersomnia due to medications or substances includes sleepiness associated with the epidemic of polypharmacy involving multiple psychotropic agents, pain medications including opioids, as well as the use of alcohol and illicit substances. Obstructive sleep apnea (OSA) is the most common intrinsic cause of sleepiness, but rarer disorders such as narcolepsy and idiopathic hypersomnia must also be considered. Periodic limb movement disorder is uncommon, as periodic limb movements, while frequently seen on polysomnograms, rarely cause sleepiness alone. Delayed sleep-wake phase disorder, the most important of the intrinsic circadian rhythm sleep-wake disorders, occurs predominantly in adolescents and young adults.



**TABLE 2-2 Causes and Assessment Tools for Hypersomnolence**

Causes	Assessment Tools
Insufficient sleep syndrome	History, sleep logs, wrist actigraphy
Hypersomnia due to medications or drugs	History, urine drug screen
Circadian rhythm sleep-wake disorders including shift work disorder	History, sleep logs, wrist actigraphy
Sleep apnea	History, diagnostic algorithms, oximetry, home sleep apnea tests, polysomnography
Narcolepsy	History, polysomnography, multiple sleep latency tests
Idiopathic hypersomnia	History, polysomnography, multiple sleep latency tests
Periodic limb movement disorder	Polysomnography
Kleine-Levin syndrome	History

Kleine-Levin syndrome is an extremely rare disorder of periods of hypersomnia lasting days to weeks and is associated with cognitive dysfunction, altered perception, eating disorders, and disinhibited behavior. It is important to be aware that some patients have more than one disorder: patients with years of chronic sleep deprivation may only present for help when they develop sleep apnea.

### Clinical Approach and Investigations

The differentiation of sleepiness and fatigue is often a useful starting point in understanding tired patients. Sleepiness is an inability to remain awake in sedentary environments; the patients' eyelids droop, neck extensor tone is lost, and microsleeps occur. In contrast, fatigue is a lack of physical energy with muscle exhaustion. Fatigued patients may have to lie down and sometimes sleep, but this is different from the sudden, brief inappropriate dozing experienced by a sleepy patient. Fatigue alone is usually not due to a primary sleep disorder (although fatigued patients may have

associated insomnia or nonrestorative sleep), but exceptions can occur, such as in some women with sleep apnea.<sup>1</sup>

The assessment of sleepiness can be approached in the following three steps (**Figure 2-1** and **Case 2-1**). Because multiple factors may interact to cause hypersomnolence, the diagnoses suggested in both steps one and two should be considered during the initial clinical assessment.

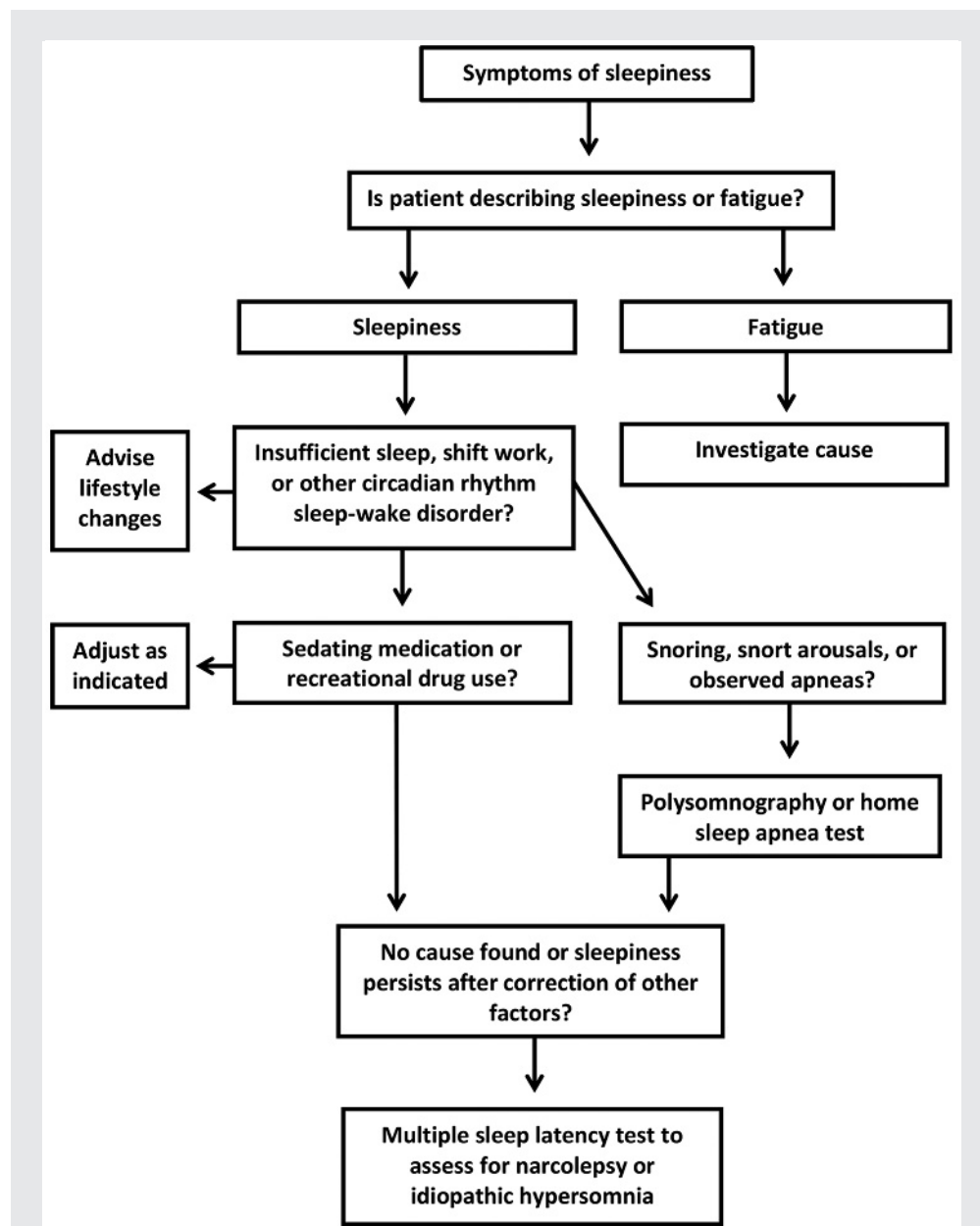
**Step one.** The clinician should consider insufficient sleep syndrome, circadian rhythm sleep-wake disorders (including shift work disorder), or the effects of drugs. All of these causes are best assessed through a history of a night's sleep. Is waking in the morning spontaneous or due to an alarm? Does the hypersomnolent patient extend sleep by sleeping in on weekends, and does the sleepiness then improve or resolve? Similarly, does sleeping as late as desired improve alertness in a patient with a late bedtime suspected of having delayed sleep-wake phase disorder? How many jobs does the patient hold, and what are the exact work schedules and their relationship to sleep times?

### KEY POINTS

- Obstructive sleep apnea is the most common intrinsic cause of sleepiness, but rarer disorders must also be considered. Periodic limb movements are frequently seen on polysomnograms, but are an uncommon cause of sleepiness unless associated with restless legs syndrome.
- Differentiating sleepiness and fatigue is important, as fatigue alone is not usually due to a primary sleep disorder. An exception is that women with sleep apnea may present with fatigue rather than sleepiness.
- The first step to diagnosing hypersomnolence is to consider insufficient sleep syndrome, shift work disorder, other circadian rhythm sleep-wake disorders, or drug effects. This is best accomplished through a history supplemented as appropriate by a sleep log, wrist actigraphy, and urine drug screens.

**KEY POINT**

■ Assessment for sleep apnea includes taking a history of snoring, snort arousals, observed apneas, and daytime sleepiness (including scales such as the Epworth Sleepiness Scale), measuring the body mass index, and a physical examination of the palate, tongue, jaw, nose, and neck.



**FIGURE 2-1** Approach to the sleepy patient.

Does the patient have a history of recreational drug use or excessive alcohol consumption?

A sleep diary kept by the patient for 1 to 2 weeks can be very helpful in assessing sleep schedules. The sleep schedule can be confirmed with the use of wrist actigraphy, a technique involving the use of an accelerometer attached to the wrist that measures

movement. Quiescent periods correlate well with episodes of sleep as defined by polysomnography. A urine drug screen may sometimes be required if undeclared drug use is suspected.

**Step two.** The clinician should consider sleep apnea. A history of snoring and observed apneas should be obtained from a bed partner or observer. Can the snoring be heard outside the

## Case 2-1

A 33-year-old man who worked as a banker presented with excessive daytime sleepiness that he had experienced since college, when he would often doze off during lectures and at his desk studying. He admitted to insufficient sleep while a student, but the hypersomnolence persisted after he started working. He found himself dozing while in his office, sitting in conferences, watching television, and reading in a chair. After driving for 20 minutes, the car frequently drifted toward the shoulder because of his sleepiness. His Epworth Sleepiness Scale score was 15. On weekdays, he went to bed at 11:15 PM and fell asleep in 15 minutes, did not wake during the night, and awoke with an alarm at 6:00 AM feeling unrefreshed. On weekends, he went to bed at about the same time, but woke up spontaneously at 8:00 AM, feeling no less tired. His wife described snoring in all positions, but had not observed apneas. He experienced a few spells of sleep paralysis on waking in the morning while at college but no hallucinations or cataplexy. He did not have symptoms of restless legs syndrome or a history of parasomnias. He had a past medical history of depression since college, and his only medication was sertraline 50 mg in the morning. He did not use tobacco or alcohol and drank only one caffeinated beverage a day.

Examination revealed a body mass index of 30.5 kg/m<sup>2</sup>, an oropharynx graded as Friedman classification grade IV with normal nose and jaw examination. Neurologic examination was normal.

He was asked to discontinue sertraline for 2 weeks under the supervision of his primary physician and to extend his time in bed to 8 hours a night for 1 week. He wore a wrist actigraph during this time, which revealed an estimated mean sleep time of 7 hours and 18 minutes. He reported no improvement in sleepiness. Therefore, polysomnography was performed, revealing a total sleep time of 430 minutes, rapid eye movement (REM) sleep latency of 87 minutes, and a respiratory disturbance index of 3 per hour. No periodic limb movements were recorded. A multiple sleep latency test the following day revealed a mean sleep latency of 3.1 minutes with REM sleep recorded within 15 minutes of sleep onset on three of the four naps. A diagnosis of narcolepsy type 2 was made.

**Comment.** In this case, multiple diagnoses were considered. His sleep time on weekdays was short, raising the question of insufficient sleep syndrome. However, extending sleep duration on weekends did not improve sleepiness. He had features to suggest possible obstructive sleep apnea, including snoring and the anatomic configuration of his oropharynx. Extending sleep time, confirmed by wrist actigraphy, did not improve alertness. Polysomnography did not confirm sleep apnea. A multiple sleep latency test performed after discontinuation of sertraline for 2 weeks established a diagnosis of narcolepsy. This diagnosis was classified as narcolepsy type 2, because the patient had no history of cataplexy. The case illustrates how a careful history and examination with stepwise use of appropriate testing can result in a definitive diagnosis.

bedroom? In which position does the patient snore? Is the patient aware of snort arousals? Does the patient have a dry mouth or headache on morning

wakening? How has the patient's weight changed with time? Does the patient have a history of upper airway or nasal surgery? How sleepy is the patient?

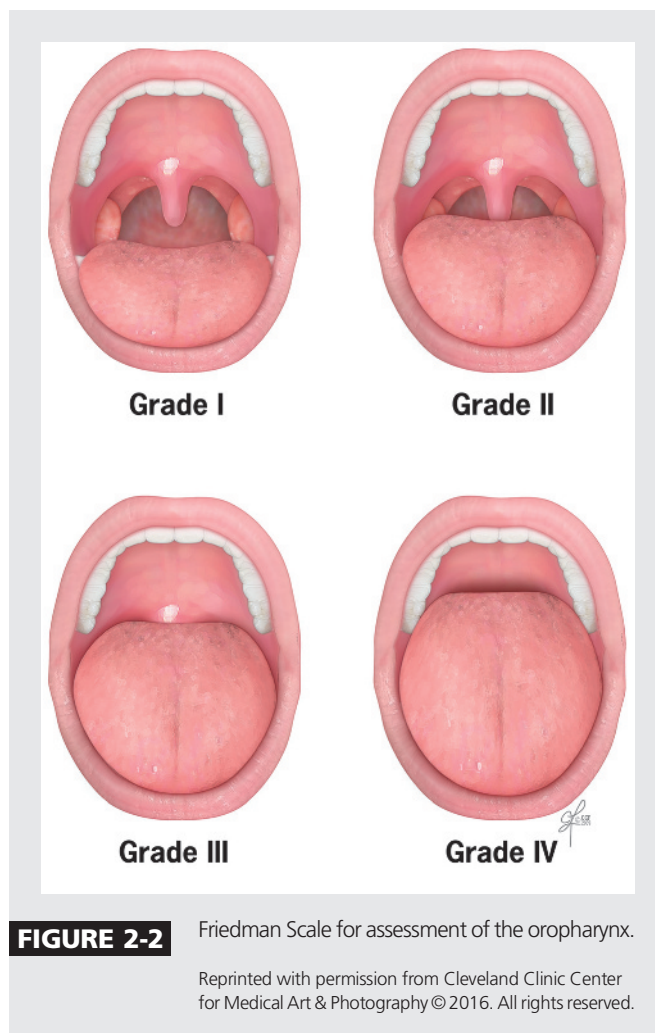


The Epworth Sleepiness Scale<sup>2</sup> (**Supplemental Digital Content Appendix**, [links.lww.com/CONT/A222](https://links.lww.com/CONT/A222)) is a useful screen for hypersomnolence, but is not specific for sleep apnea. The maximum score is 24; values above 10 are considered to represent hypersomnolence.

The patient's body mass index should be calculated. The upper airway should be examined, noting the relationship of the tongue to the uvula and soft palate using the Friedman classification (**Figure 2-2**) as well as the size of the tonsils and the diameter of the oropharynx. Any nasal obstruction should be assessed. The configuration of the jaw and teeth should be noted and assessed for

overbite or overjet. Any physical signs suggestive of an endocrinopathy such as hypothyroidism, acromegaly, or polycystic ovary syndrome should be noted.

Various validated algorithms have been developed as screening tools to predict the presence of OSA. These use different factors such as age, sex, history of snoring, observed apneas or snorts, daytime sleepiness, presence of hypertension, body mass index, and size of the neck to provide weighted total scores. They include the STOP-BANG Questionnaire,<sup>3</sup> Berlin Questionnaire,<sup>4</sup> and the Flemons Sleep Apnea Clinical Score.<sup>5</sup> Overnight pulse oximetry is sometimes used as a screening test to identify patients



who warrant a sleep study. However, both false positives and false negatives may occur, and the test is best used in limited circumstances to prioritize patients for urgent sleep studies when the oxyhemoglobin desaturation index is very high or when severe hypoxemia is detected.

For a definitive diagnosis of sleep apnea, either laboratory polysomnography or home sleep apnea testing may be performed. In laboratory polysomnography, the EEG is monitored with a minimum of three derivations, recording activity over the frontal, central, and occipital head regions, together with recording of eye movements (electrooculogram) and submental and anterior tibial EMG. Respiratory monitoring includes surrogate measures of nasal airflow by nasal pressure transducers and oronasal thermocouples, chest and abdominal plethysmography, pulse oximetry, and recording of upper airway sound. Body position and ECG are also recorded, and audiovisual monitoring is available. Home sleep apnea testing involves only the cardiorespiratory monitoring modalities. The advantages of laboratory polysomnography are the availability of the technologist to maintain the integrity of the system and to introduce treatment such as continuous positive airway pressure during the study, the ability to determine the time actually asleep and the different stages of sleep, and the ability to record abnormal movements. Home sleep apnea testing, in contrast, allows more natural sleep in the patient's home and is considerably cheaper. Home sleep apnea testing is indicated for patients with a high pretest probability of moderate or severe OSA in the absence of comorbidities such as cardiac failure, severe chronic obstructive pulmonary disease, dement-

tia, or neuromuscular diseases affecting breathing.<sup>6</sup> Studies have demonstrated that the adherence to treatment is no different in patients undergoing home sleep apnea testing compared to laboratory polysomnography, as long as they are followed by experienced sleep specialists in academic sleep centers.<sup>7,8</sup>

**Step three.** Once sleep-disordered breathing has been ruled out clinically or by appropriate tests, the next step is to determine whether the sleepy patient has a central disorder of hypersomnolence such as narcolepsy or idiopathic hypersomnia. Narcolepsy type 1 is suspected if the patient gives a history suggesting cataplexy, which is characterized by brief episodes of transient muscle weakness precipitated by emotions, usually positive, and, almost always on some occasions, by laughter. Weakness may be generalized or partial and involve only the facial or lower extremity muscles. Consciousness is retained. Sleep paralysis and hypnagogic hallucinations are common in narcolepsy but are nonspecific, as they may also occur in subjects without narcolepsy and in patients with other sleep disorders. Sleep in patients with idiopathic hypersomnia is often long and deep, with severe sleep inertia on being woken in the morning and lengthy, unrefreshing daytime naps. However, the diagnosis of these disorders cannot be made on history alone, and further testing is essential.

The standard test for central disorders of hypersomnolence is the MSLT, in which the patient is given four or five opportunities to sleep at 2-hour intervals during the day.<sup>9</sup> The time from lights out until the first epoch of any stage of sleep is measured, and the mean sleep latency is generated. Each nap opportunity is stopped after 20 minutes without sleep and given an

#### KEY POINT

■ Indications for home sleep apnea testing are a high pretest probability of moderate or severe obstructive sleep apnea in the absence of comorbidities such as cardiac failure, severe chronic obstructive pulmonary disease, dementia, or neuromuscular diseases affecting breathing.

# KEY POINTS

- A short mean sleep latency (8 minutes or fewer) and two or more sleep-onset rapid eye movement periods on a multiple sleep latency test suggest narcolepsy, but only if patients have adequate sleep length and normal circadian rhythmicity for at least 1 week and have discontinued psychotropic medications for at least 2 weeks.
- Because of low specificity for the diagnosis of narcolepsy, testing for the human leukocyte antigen DQB1\*0602 should be restricted to patients in whom a spinal tap for measurement of CSF hypocretin-1 concentration is contemplated.

arbitrary latency of 20 minutes for the purpose of the calculation of mean latency. A mean latency of greater than 10 minutes is considered normal alertness, and a mean latency of fewer than 5 minutes is considered pathologic hypersomnolence. Latencies between 5 and 10 minutes fall in an overlap zone, with the shorter the latency, the greater the probability of a disorder of hypersomnolence. Although a mean sleep latency of 8 minutes or fewer is one of the formal criteria for the diagnosis of narcolepsy, this should not be regarded as a cutoff value between normal and abnormal. Patients who fall asleep within 20 minutes of lights out are allowed to sleep for 15 minutes before being awakened. Entering REM sleep during this time in at least two naps (or one nap if the patient had a REM latency of 15 minutes or fewer on the preceding night polysomnogram) is suggestive of narcolepsy in the correct clinical setting.

It is important to understand that the findings on an MSLT are non-specific and can only be accurately interpreted if the circumstances surrounding the test are meticulously controlled. In population-based studies with subjects not selected for sleep problems,<sup>10–12</sup> two or more sleep-onset REM periods occurred in 3.9% to 13.1% of subjects, more commonly in men. In different studies, sleep-onset REM periods were associated with shift work, shorter sleep on the night before the MSLT, and lower nocturnal oxyhemoglobin saturation. It is thus essential to ensure that patients have adequate length of sleep and normal circadian rhythmicity for at least 1 week before the test. A minimum time of 7 hours in bed each night is necessary, with laboratory polysomnography performed the night before the MSLT. Sleep time should

be monitored by wrist actigraphy for at least 1 week prior, complimented by the patient keeping a sleep log. In addition, all psychotropic, sedating, and REM suppressant medications should be stopped the greater of 2 weeks or 5 half-lives before the MSLT. If this cannot be safely done, then it is better not to perform the MSLT and to rely on other approaches for diagnosis.

An alternative approach to the diagnosis of narcolepsy in selected cases may be the measurement of CSF hypocretin-1 (orexin-A) concentration. CSF hypocretin-1 levels are low in 90% to 95% of patients with narcolepsy with cataplexy and in 24% to 32% of those having narcolepsy without cataplexy.<sup>13,14</sup> For patients with a clinical diagnosis of cataplexy, the test may be helpful if an MSLT cannot be accurately interpreted, such as in the setting of untreated sleep apnea or confounding medications that cannot be safely discontinued. The test is currently only available in a few research laboratories. Essentially, all patients with narcolepsy who have low CSF hypocretin-1 concentrations also carry the human leukocyte antigen (HLA) DQB1\*0602; therefore, assessment of HLA status should precede a spinal tap.<sup>13–15</sup> Patients who are negative for this tissue type should not have lumbar punctures performed, as hypocretin-1 levels will inevitably be normal. In patients suspected of having narcolepsy, little other indication for HLA testing exists, as approximately 20% of the population are DQB1\*0602 positive, resulting in the test having very low specificity for the diagnosis.

## THE PATIENT WITH NEUROMUSCULAR DISORDERS

Diaphragmatic dysfunction in neuromuscular disorders often manifests

initially as sleep-disordered breathing at night, especially during REM sleep. The diaphragm is the major muscle responsible for inspiration, especially during REM sleep, when the intercostal and upper airway muscles become atonic. Secondary alterations can occur in central respiratory drive, sometimes with the development of chest wall restriction from scoliosis. The most common neuromuscular disorders seen in a sleep center are amyotrophic lateral sclerosis, muscular dystrophies (especially Duchenne muscular dystrophy and myotonic dystrophy), and bilateral phrenic neuropathies, but occasionally patients with inflammatory muscle diseases, myasthenia gravis, and polyneuropathies may also develop respiratory failure.<sup>16</sup> Neurologists should be familiar with the assessment of the respiratory system in patients with these disorders to determine when intervention may be needed. As many of these disorders are progressive, respiratory assessments should be a routine part of such patients' follow-up care.

### Clinical Approach

The most important history to obtain is whether the patient becomes dyspneic lying flat during wakefulness or sleep. Dyspnea may also develop with effort, especially when climbing stairs.

Breathing should be assessed while sitting up and supine, and the patient should be asked to remove clothing from the chest to clearly visualize abdominal and chest movement. Diaphragm dysfunction results in paradoxical movement of the abdomen and chest when the patient lies flat. Instead of the abdomen expanding with inspiration in synchrony with the chest, it pulls inward. The respiratory rate may increase with supine breathing, and accessory respiratory muscles may be activated. If available, a pulse oximeter

may show a reduction in oxyhemoglobin saturation in the supine position. Chest expansion and the use of accessory muscles should be assessed. It may also be helpful to ask the patient to cough as loudly as possible, as a reduced volume cough may give an approximate indication of reduced respiratory muscle strength. Counting aloud on a single deep breath can also be a useful bedside test, as most patients with normal tidal volume and breath support can count to the high twenties or thirties on a single breath, while patients with neuromuscular weakness of the diaphragm often cannot exceed counting to 20.

### Investigations

Diagnostic tests may include electrophysiologic studies of the diaphragm such as phrenic nerve conduction studies and needle EMG, often combined with ultrasound assessment.<sup>17</sup> Overnight pulse oximetry is a very helpful screening tool for early respiratory decompensation during sleep. Initially, this may show cyclical drops in saturation for four to six periods per night, presumably corresponding to periods of REM sleep with superimposed oscillations of signal representing REM-related apneas or hypopneas, often central in origin (**Figure 2-3**). Later, more persistent hypoxemia may develop. Pulmonary function tests, including vital capacity, and maximal inspiratory and expiratory pressures should be obtained, and arterial blood gas measurements for daytime retention of carbon dioxide may be helpful. Laboratory polysomnography may be needed to assess optimal management with bilevel positive airway pressure.

### THE PATIENT WITH RESTLESS LEGS SYNDROME

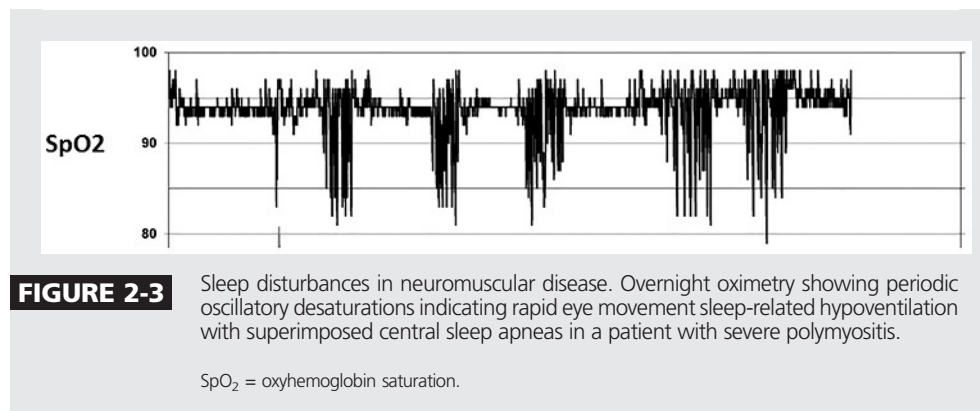
Restless legs syndrome (RLS), causing at least moderate distress and occurring at least twice a week, has a

#### KEY POINT

■ Patients with neuromuscular disorders should be assessed for respiratory dysfunction at all visits. Clinical screening assessments include inquiring about orthopnea and observing for paradoxical diaphragmatic movement in the supine position. Overnight oximetry may show early rapid eye movement sleep-related oxyhemoglobin desaturations.

### KEY POINTS

- Restless legs syndrome is diagnosed clinically by a history of an urge to move, often associated with leg discomfort, that comes on at rest, is relieved at least temporarily by movement, and is worse in the evening or at night.
- Serum ferritin should be checked in patients with restless legs syndrome, but other tests such as polysomnography or routine nerve conduction study and EMG are generally not indicated.



prevalence of 2% to 3%. RLS is more common in women than men, and the prevalence increases with age. Neurologists are frequently requested to diagnose and treat this common disorder.

### Clinical Approach

The diagnosis of RLS is based on an accurate history. Patients must describe an urge to move the legs usually, but not always, accompanied by a discomfort in the affected limbs. While typically this takes the form of a creepy-crawly sensation, it can sometimes be described as burning, tingling, aching, or an indescribable deep discomfort. The urge to move should arise while the patient is at rest, should be relieved by movement such as walking as long as the activity continues, and is generally worse or present only in the evening or during the night.<sup>18</sup> Care should be taken to exclude common conditions that can mimic RLS.<sup>19</sup> Leg cramps are painful with palpable contractions in the affected muscles and are relieved by stretching or massaging the muscle rather than walking. Positional discomfort in a limb at night is relieved by changing position and does not require walking. Habitual foot tapping is a subconscious habit easily stopped when the patient is made aware of it.

The subsequent history should be focused on possible etiologies. Any family history of RLS should be noted.

As iron deficiency is an important cause of RLS, patients should be asked about fresh rectal bleeding, melena, dyspepsia, menorrhagia, frequent blood donations, and vegan diets. Any symptoms of peripheral neuropathy should be elicited. As RLS may be associated with antidepressant use, determining any relationship between their initial prescription and the onset of RLS may be helpful. If the patient has been treated with dopaminergic medications in the past, it is important to compare the time of symptom onset before and after introduction of the drugs, as dopamine agonists can cause RLS augmentation, primarily characterized by an earlier onset of symptoms.<sup>20</sup> Neurologic examination rarely provides useful information, but evidence for a peripheral neuropathy should be sought.

### Investigations

Polysomnography is not indicated for patients with suspected RLS, unless sleep apnea is also being considered, as the presence of periodic limb movements of sleep is neither specific nor sensitive for the diagnosis. Conversely, periodic limb movements are nonspecific findings, and their incidental presence on a polysomnogram does not imply that the patient has RLS. Serum ferritin should be measured in all patients with at least moderately severe RLS. If the patient



has an acute or chronic inflammatory disorder, transferrin saturation should also be assessed, as serum ferritin is an acute phase reactant resulting in the possibility of falsely elevated levels despite iron deficiency.<sup>21</sup> Unless other clinical indications of specific vitamin deficiencies are evident, serum folate or vitamin B<sub>12</sub> concentrations do not need to be assessed. Renal failure rarely presents with RLS, so routine measurement of kidney function in all patients with RLS is not required. Nerve conduction studies and EMG are not indicated unless clinical suspicion of a peripheral neuropathy is present.

### **THE YOUNG PATIENT WITH ABNORMAL MOVEMENTS DURING SLEEP**

Abnormal motor activity in a child or young adult may have many causes. Simple repetitive movements may be due to periodic limb movement disorder or rhythmic movement disorder. Most episodes of recurrent complex behaviors prove to be either due to arousal disorders from non-REM sleep or nocturnal seizures, although, occasionally, sleep-related dissociative disorder and REM sleep behavior disorder (RBD) may occur. Disorders of arousal from non-REM sleep comprise a spectrum of behaviors known as sleepwalking, sleep terrors, and confusional arousals. Focal seizures during sleep can have varied manifestations and degrees of disturbance of consciousness, depending on the site of origin of the epileptic discharges.

#### **Clinical Approach**

A careful description should be obtained from both the patient and observers, understanding that they may perceive the events very differently. If the events are strongly stereotyped, seizures are more likely than parasomnias. This is especially true if

similar events also occur during wakefulness. Arousal disorders arise from non-REM sleep and so are most common in the first one-third of the night, whereas seizures can occur at any time. Seizures generally last less than a minute, whereas episodes of sleepwalking can last longer. Descriptive features suggestive of seizures include clonic movements, facial and limb automatisms, dystonic limb posturing, or hypermotor behaviors such as pelvic thrusting and bicycling movements.<sup>22</sup> In contrast, sleep terrors are characterized by intense vocalizations associated with sitting up in bed and sleepwalking by quiet standing or walking. However, some forms of focal seizures can also involve nocturnal wanderings. Enuresis is unusual during arousal parasomnias but is common during generalized seizures. Consciousness is usually reduced in arousal disorders and seizures of temporal lobe origin, whereas it is often preserved without postictal confusion in nocturnal seizures arising from the frontal lobes. Rhythmic movement disorder is characterized by regular repetitive movements such as body rocking, head shaking, or thumping of both legs. Periodic limb movements consist of regular flexion of one or both legs at intervals of 5 to 90 seconds. As they are often associated with RLS, any urge to move the legs should be explored. In young children, age-appropriate descriptors may be needed, such as “spiders,” “owies,” or “tickles.” Any family history of seizures or arousal parasomnias should be elucidated, as well as any risk factors for epilepsy, such as birth events, head injuries, febrile seizures, or meningoen- cephalitis. Possible precipitants for sleepwalking should be identified, such as sleep deprivation, febrile illnesses, or environmental noise. A full neurologic examination should be performed to identify any signs of focal brain disease.

#### **KEY POINT**

■ Complex nocturnal motor behaviors in a child or young adult are usually due to seizures or a non-rapid eye movement arousal parasomnia such as sleepwalking. Events that are stereotypical are more likely to be seizures.

**KEY POINTS**

- Polysomnography to elucidate nocturnal spells should include 16 EEG derivations and video recordings. The video associated with each arousal should be reviewed, as confusional arousals can otherwise be missed.
- Collateral history from a bed partner or caregiver is essential for the diagnosis of rapid eye movement sleep behavior disorder. Symptoms suggesting a synucleinopathy should also be elicited, and the patient should be examined for signs of parkinsonism, cognitive impairment, or dysautonomia.

**Investigations**

In children, a diagnosis of sleepwalking or sleep terrors can often be made on history alone. However, when doubt exists regarding the diagnosis or the events have resulted in injury, further investigations are needed. A wake and sleep EEG and MRI scan of the head should be obtained. It is often necessary to record actual events to reach a definitive diagnosis. If the neurologist considers the probability of seizures to be higher than parasomnias, then admission to an epilepsy monitoring unit is appropriate. However, if parasomnias are more likely and occur at an appropriate frequency, then polysomnography with an additional 16 EEG derivations, arm surface EMG, and time-synchronized video and audio recording is indicated. It is important to ask the patient to inform the technologist if an event has occurred, as some may be minor and otherwise hard to subsequently locate on the recording. Both the video and the EEG at the time of events should be carefully reviewed. Seizures occur predominantly during non-REM sleep stages N1 and N2, whereas arousal disorders arise from sleep stage N3.<sup>23</sup> Nocturnal frontal lobe seizures often have no surface EEG changes, so attention to the clinical phenomenology may be most important in reaching a diagnosis. The video associated with all arousals from sleep stage N3 should be reviewed, as some minor confusional arousals that might establish a diagnosis of an arousal disorder may otherwise be missed. Arousal disorders from non-REM sleep do not have specific polysomnographic appearances, and the diagnosis relies predominantly on review of the recorded behaviors. Sleep deprivation the night before the study may increase the probability of inducing both seizures and arousal disorders. Making

a deliberate loud noise near the patient during sleep stage N3 has been reported to precipitate abnormal arousals.

**THE OLDER PATIENT WITH ABNORMAL MOVEMENTS DURING SLEEP**

RBD predominantly affects middle-aged and older patients, of whom approximately 80% are men. An important and close relationship exists between RBD and synucleinopathies, with 15% to 65% of patients with Parkinson disease, 68% to 80% of those with dementia with Lewy bodies, and 60% to 90% of those with multiple system atrophy (MSA) exhibiting RBD.<sup>24</sup> The risk of phenocconversion from idiopathic RBD to parkinsonism or dementia may be as high as 75% 10 years after RBD diagnosis.<sup>25,26</sup> Especially in younger patients, antidepressant use may be associated with RBD.<sup>27</sup> RBD is also commonly seen in patients with narcolepsy.

**Clinical Approach**

Collateral history from a bed partner or caregiver is essential for establishing a diagnosis of RBD. The patient is typically described as punching or flailing the arms, thrashing in bed, kicking the legs, and vocalizing (usually shouting). Bed partners are often inadvertently injured, and the patient can fall out of bed with resultant abrasions, lacerations, ecchymoses, and fractures. Ambulation is unusual, but may occur in 11% of patients.<sup>28</sup> The movements vary between episodes and do not have the stereotyped quality of seizures. Urination does not occur. Dream enactment episodes in RBD occur usually in the second half of the night. If the patient is awakened, a description of dream content can often be obtained, with the most common theme being defense against attack.<sup>29</sup>

A history of snoring, snort arousals, or observed apneas should be elicited.

OSA may mimic RBD, with abnormal behavior at the time of the arousals terminating apneas. Additionally, OSA is common in older men, the same population that develops RBD, and is especially common in patients with MSA. It is also important to ask about the occurrence of nocturnal stridor, as the combination of definite stridor and RBD is almost diagnostic of MSA and is not seen in Parkinson disease.<sup>30</sup> Stridor is described as a harsh, high-pitched inspiratory sound different from snoring. It sometimes helps if the neurologist can mimic the two sounds, but many observers still have difficulty differentiating them, and an audio recording of the patient on a smartphone is often helpful.

If RBD is suspected, the patient and partner or caregiver should be questioned about symptoms that would suggest the presence of a neurodegenerative disorder or a possible prodrome of a synucleinopathy. Topics that should be covered include tremor, handwriting, speech, gait unsteadiness and falls, lightheadedness, sphincter and sexual function, smell, cognitive status (memory, direction finding, judgment), and hallucinations. Like RBD, anosmia and chronic constipation may be very early manifestations of Lewy body diseases. The presence of abnormal olfaction, for instance, increases the risk of phenoconversion in a patient with otherwise isolated RBD by a hazard ratio of 2.3.<sup>31</sup> Conversely, any patients with diagnosed or suspected Parkinson disease, dementia with Lewy bodies, or MSA should be questioned about dream enactment behaviors, symptoms of sleep apnea, and stridor.

Neurologic examination in patients with RBD should concentrate on a clinical assessment of mental function, testing for orthostatic hypotension, and assessment for subtle or overt

signs of parkinsonism or dementia. At the least, this should include assessing for tremor and testing eye movements; speech; muscle tone; rapid alternating movement rate of the tongue, hands, fingers, and feet; and the finger-nose and heel-knee test. Gait should be checked, including tandem walking, and the pull test should be performed to assess for postural stability. Sometimes soft signs of cogwheel rigidity at one wrist can be elicited with reinforcement, or primitive reflexes, such as a persistent glabellar reflex, snout, or palmomental reflex may be found at a younger age than normally seen.

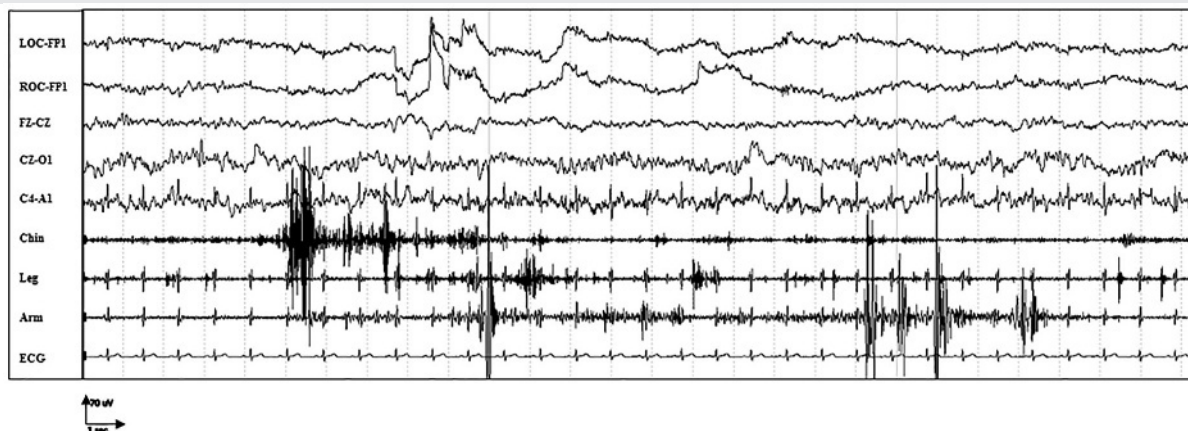
### Investigations

If RBD is suspected, polysomnography should be performed to confirm the diagnosis. This is necessary because sleep apnea may be present either as a comorbidity or as an alternative explanation of the motor activity, and because the serious implications of the disorder mandate a definitive diagnosis. Polysomnography for the evaluation of RBD should include at least one upper extremity surface EMG derivation, such as extensor digitorum communis or flexor digitorum superficialis,<sup>32</sup> in addition to the conventional recordings from the anterior tibial and the submental muscles (**Figure 2-4**<sup>33</sup>). Additional EEG derivations should be added if suspicion exists of a possible seizure disorder. Time-synchronized video and audio recordings are essential, and any episode of increased muscle activity should be carefully reviewed. In addition to either a history of dream enactment behavior or such behavior observed during polysomnography, a diagnosis of RBD requires loss of REM sleep atonia with either increased phasic or persistent tonic activity. Whether muscle tone is abnormal in REM sleep is usually

### KEY POINT

- The diagnosis of rapid eye movement sleep behavior disorder requires polysomnography with submental, arm, and anterior tibial EMG derivations, and video to record any dream enactment behaviors.



**FIGURE 2-4**

Rapid eye movement (REM) sleep without atonia. This is a 30-second fragment of a polysomnogram illustrating REM sleep with increased muscle activity (REM sleep without atonia) in the submental, anterior tibial, and extensor digitorum communis EMG derivations. In the presence of dream enactment behavior, these findings are diagnostic of REM sleep behavior disorder.

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determined by experienced sleep specialists subjectively assessing the record. Normative data, however, are available.<sup>34,35</sup>

Additional neurologic tests will depend on the clinical scenario. If symptoms suggest autonomic dysfunction, autonomic testing, including a thermoregulatory sweat test, may be helpful. Neuropsychometric testing

may better characterize perceived cognitive problems. Abnormalities on dopamine transporter single-photon emission computed tomography (SPECT) scans and objective tests of smell and color vision have experimentally been shown to predict phenoconversion in patients with RBD, but are not used routinely in clinical practice (Case 2-2).<sup>36</sup>

## Case 2-2

A 59-year-old man presented with strange behaviors at night that he had been experiencing for the last year. His wife described him flailing his arms, kicking, and shouting at least 3 times a week. On occasion, he had hit her, once leaving a bruise. He had fallen out of bed several times, once injuring his shoulder. When woken during an episode, he described dreams of being attacked by unknown assailants. He did not snore. He had lost much of his sense of smell about 10 years earlier, which he ascribed to a nasal infection. He had no other neurologic symptoms.

Neurologic examination was normal apart from a nonfatiguing glabellar reflex and positive palmomental reflexes. He had reduced arm swing on the left when walking.

Polysomnography with additional extensor digitorum communis surface EMG showed loss of normal muscle atonia during rapid eye movement (REM) sleep, with the patient vocalizing and punching in the air. Respiration was normal.

*Continued on page 987*

*Continued from page 986*

A diagnosis of REM sleep behavior disorder was made, and melatonin was prescribed. At a nightly dose of 9 mg, most dream enactment behavior resolved. Neurologic examination 1 year later revealed a mild rest tremor of the left hand and cogwheel rigidity at the left wrist elicited only when he was asked to simultaneously move his right arm.

**Comment.** This case indicates how REM sleep behavior disorder and anosmia can precede phenoconversion to a clinical synucleinopathy, sometimes by years. At presentation, the patient exhibited minor neurologic signs insufficient to diagnose parkinsonism, but a year later it was possible to confirm a diagnosis of Parkinson disease.

## CONCLUSION

Sleep medicine remains a clinical specialty. Diagnoses can often be made by taking meticulous histories and obtaining collateral information from observers. Investigations should be used judiciously in a stepwise fashion and interpreted in the setting of the clinical problem. A holistic approach to the patient is necessary, integrating physical and psychosocial factors and not overrelying on the quantitative results of sleep studies in isolation from the patient's overall problem. Reaching the correct diagnoses of sleep disorders can be very satisfying experiences for the physician and patient as they often lead to long-lasting and effective management strategies.

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# Narcolepsy and Other Central Hypersomnias

Yves Dauvilliers, MD, PhD; Lucie Barateau, MD

## ABSTRACT

**Purpose of Review:** This article focuses on the clinical presentation, pathophysiology, diagnosis, differential diagnosis, and management of narcolepsy type 1 and narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, and other central disorders of hypersomnolence, as defined in the *International Classification of Sleep Disorders, Third Edition (ICSD-3)*.

**Recent Findings:** In *ICSD-3*, the names of some central disorders of hypersomnolence have been changed: narcolepsy with cataplexy and narcolepsy without cataplexy have been renamed narcolepsy type 1 and narcolepsy type 2, respectively. A low level of hypocretin-1/orexin-A in the CSF is now theoretically sufficient to diagnose narcolepsy type 1, as it is a highly specific and sensitive biomarker. Conversely, other central hypersomnias are less well-defined disorders with variability in the phenotype, and few reliable biomarkers have been discovered so far. The epidemiologic observation that influenza A (H1N1) infection and vaccination are potential triggering factors of narcolepsy type 1 (discovered during the 2009 H1N1 pandemic) has increased interest in this rare disease, and progress is being made to better understand the process (highly suspected to be autoimmune) responsible for the destruction of hypocretin neurons. Treatment of narcolepsy remains largely symptomatic, usually initially with modafinil or armodafinil or with higher-potency stimulants such as methylphenidate or amphetamines. Several newer wake-promoting agents and psychostimulants have also been developed, including sodium oxybate, which has a role in the treatment of cataplexy and as an adjunctive wake-promoting agent, and pitolisant, a selective histamine H<sub>3</sub> receptor inverse agonist that is currently only available in Europe.

**Summary:** Although far less common than many other sleep disorders, central hypersomnias are among the most severe and disabling diseases in the field of sleep medicine, and their early recognition is of major importance for patients, especially children, to maximize their quality of life and functioning in activities of daily living.

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## INTRODUCTION

Excessive daytime sleepiness is the most common presenting symptom of rare sleep diseases, the hypersomnia disorders of central origin. These include narcolepsy type 1 and narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, and other hypersomnias (eg, due to a medical disorder or substance or associated with psychiatric disorders). Our understanding of the pathophysiology of central

hypersomnias has improved considerably over the past 2 decades because of the integration of data from human and animal models. The diagnostic workup includes medical history, sleep logs, and polysomnography, followed by the multiple sleep latency test in most patients and, in some, additional evaluation with actigraphy, human leukocyte antigen (HLA) genotyping, and CSF examination for hypocretin. The current management of hypersomnias of



**KEY POINT**

■ Narcolepsy type 1 is a well-defined entity characterized by excessive daytime sleepiness and cataplexy, whereas narcolepsy type 2 is a syndrome of sleepiness without cataplexy and is a considerably less specific and more heterogeneous syndrome.

central origin remains symptomatic, and good evidence for treatment (Level A) currently exists only for narcolepsy. This article reviews the clinical features, pathophysiology, diagnostic criteria, and treatment options for narcolepsy and other primary hypersomnias.

**NARCOLEPSY TYPE 1 AND TYPE 2**

Narcolepsy is classified into two distinct disorders according to the *International Classification of Sleep Disorders, Third Edition (ICSD-3)*: narcolepsy type 1, formerly called *narcolepsy with cataplexy*, and narcolepsy type 2.<sup>1</sup> Narcolepsy type 1 affects about 1 in 2000 people in the world, with a bimodal age at onset, usually between 15 and 35 years of age.<sup>2</sup> The prevalence of narcolepsy type 2 remains unclear, as this disorder is more heterogeneous, with an unknown pathophysiologic mechanism.<sup>3,4</sup>

**Clinical Features**

Excessive daytime sleepiness is the major and most frequent initial symptom of narcolepsy. Excessive daytime sleepiness arises preferentially in monotonous situations or during periods of relative inactivity. Typically, naps are short and considered to be refreshing by patients, who may also recall the experience of dream activity just after falling asleep. Similarly, nocturnal sleep is usually considered refreshing, and morning waking is usually not difficult. In children, the phenotype can be slightly different: naps are inconsistently refreshing, patients sometimes fight against sleepiness and do not fall sleep, and they may present with hyperactive behavioral symptoms that can mimic attention deficit hyperactivity disorder. During episodes of sleepiness, automatic activities (ie, saying something inappropriate or out of context in a

conversation, writing something inappropriate or illegible, or doing an activity such as driving to an inappropriate location with no memory of the event) can be seen.

Cataplexy is the pathognomonic symptom of narcolepsy type 1, defined by a loss of muscle tone in full consciousness triggered by emotions, particularly positive ones such as laughter or surprise (**Case 3-1**).<sup>5</sup> Cataplexy can either be generalized and lead to falls or partial, with lower limb collapse, head dropping, or dysarthria. Muscle stretch reflexes are abolished during generalized cataplexy, since the pathophysiology of cataplexy seems mediated by an intrusion of physiologic rapid eye movement (REM) sleep atonia into wakefulness, thereby interrupting conscious voluntary motor activity and waking muscle tone. Cataplectic attacks can be different in children. Sometimes they appear without a specific triggering factor; they can also arise in anticipation of a strong emotion to come and sometimes even during movement. Children can also present with cataplectic facial expressions, such as generalized face hypotonia, abnormal movements, and tongue protrusion.<sup>6</sup> Clinical signs and biological markers that should make the physician reconsider the diagnosis of supposed cataplectic attacks are listed in **Table 3-1**.

Other symptoms are often associated with narcolepsy, but they are not specific to the condition. Sleep paralysis is a transient paralysis lasting a few seconds or minutes while falling asleep or upon awakening. Hypnagogic (ie, while falling asleep) and hypnopompic (ie, upon awakening) hallucinations can occur at the same time as the paralysis and can be very frightening. These symptoms are also reported in the general population but are more frequent and severe in

## Case 3-1

An 18-year-old man presented with a 2-year history of severe excessive daytime sleepiness that began a few months after a vaccination for influenza A (H1N1). He had to repeat a school year because of the excessive daytime sleepiness. He was overweight and had frequent sleep paralysis and nightmares. Six months after the onset of excessive daytime sleepiness, he developed episodes of weakness in his limbs and neck triggered by various emotional stimuli, especially when he laughed with his brother. The frequency was variable, from several episodes per day to several per week, depending on exposure to the stimuli. His brother had made a cell phone video that the neurologist was able to view, which led to the diagnosis of typical cataplectic attacks.

After reviewing the patient's sleep diary to ensure he was getting adequate nocturnal sleep, polysomnography was performed, followed by a multiple sleep latency test that showed fragmented sleep with no apnea, short sleep latency (2 minutes), and four sleep-onset rapid eye movement (REM) periods, confirming a clear-cut diagnosis of narcolepsy type 1.

Human leukocyte antigen genotyping was positive for the DQB1\*0602 allele, and CSF hypocretin-1 levels in the CSF were undetectable (less than 10 pg/mL).

A modafinil treatment trial was started, with the dosage gradually increased to 200 mg in the morning and 200 mg at noon. Anticatataplectic treatment (venlafaxine 37.5 mg/d) was introduced a few weeks later, with excellent efficacy.

**Comment.** In this case, the patient's cataplectic attacks were typical, but sometimes the recognition of this pathognomonic symptom can be more difficult. Identification of cataplexy during consultation or hospitalization or video recorded by relatives helps determine if the phenotype is typical or atypical. The first-line option for excessive daytime sleepiness should be modafinil (doses from 100 mg/d to 400 mg/d). Once adequate improvement of excessive daytime sleepiness is obtained, the cataplexy severity is evaluated and treatment started, if needed. The management of excessive daytime sleepiness alone sometimes improves cataplexy. This case also illustrates the burden of narcolepsy and the impact of a delayed diagnosis on scholastic performance.

patients with narcolepsy. Nighttime sleep is altered and fragmented, with multiple nocturnal arousals and sometimes significant sleep maintenance insomnia. REM sleep behavior disorder, a parasomnia characterized by a loss of normal skeletal muscle atonia during REM sleep, has an increased frequency in narcolepsy type 1, leading to abnormal behaviors and dream enactment. An increase in weight is frequent at disease onset, especially in children (30% of all patients with narcolepsy are obese, and up to 50%

of children with narcolepsy are obese). Children may also experience precocious puberty.

Narcolepsy type 1 is a chronic disease with an often stable clinical course. The severity of cataplexy and sleepiness may improve with age, whereas nighttime sleep may worsen. In contrast, the clinical course of narcolepsy type 2 remains unclear. Some patients may later develop cataplexy and be reclassified as having narcolepsy type 1; other patients with narcolepsy type 2 may have a chronic

**KEY POINT**

■ Pathophysiologic studies have shown that narcolepsy type 1 is caused by the early loss of neurons in the hypothalamus that produce hypocretin/orexin.

**TABLE 3-1 Clinical Signs and Biological Markers of Typical Cataplexy and Atypical Attacks Suggesting an Alternative Diagnosis**

► **Typical Cataplexy**

Clinical signs

Clear positive emotional trigger (eg, laughter, telling a joke, surprise)  
Frequent attacks (multiple times per day or week)  
Brief duration (seconds to 1–2 minutes)  
Consciousness preserved  
Generalized or segmental (face, head/neck, knee dropping/buckling with or without falling)

Biological markers

Presence of HLA DQB1\*0602 allele  
Low hypocretin-1 levels in the CSF (<110 ng/L)

► **Atypical Attacks<sup>a</sup>**

Clinical signs

Rarity of attacks (<1/year)  
Nonrecurrence despite the absence of treatment  
Long lasting (>2 minutes)  
Alteration of consciousness  
Unilateral or asymmetric localization  
Affecting only the upper limbs (not the face, neck, or lower limbs)  
No association with emotional triggers (except in children)  
Relatives and people nearby do not notice the episodes  
Only triggered by negative stimuli and emotion (eg, anger, fear, stress)  
Prodromal symptoms or occurrence of symptoms after the episode of any kind (eg, warm feeling, sweat, dizziness, tinnitus, visual and auditory impairment, nausea, tingling sensation in the extremities)

Biological markers

Absence of HLA DQB1\*0602 allele  
Normal hypocretin-1 levels in the CSF (>200 ng/L)

CSF = cerebrospinal fluid; HLA = human leukocyte antigen.

<sup>a</sup> These clinical signs and biomarkers suggest an alternative diagnosis.

stable condition. In approximately one-half of patients with narcolepsy type 2, excessive daytime sleepiness may improve spontaneously, without the persistent neurophysiologic hallmarks of narcolepsy.<sup>7</sup>

### Pathophysiology

Narcolepsy type 1 is caused by a selective loss of a small population of neurons in the lateral hypothalamus that synthesize hypocretin neuro-

peptides.<sup>8</sup> Hypocretin-1/orexin-A and hypocretin-2/orexin-B are neurotransmitters that were discovered 20 years ago.<sup>9,10</sup> Several genetic animal models of the disease exist, as across species (in both mice and dogs), disrupted hypocretin signaling leads to a narcoleptic phenotype with excessive daytime sleepiness and cataplexy.<sup>11</sup> Recently, hypocretin neurons were shown to be particularly susceptible to influenza A (H1N1) viral infection in



mice lacking B and T cells, and hypocretin neurons were destroyed after injection of autoreactive cytotoxic CD8<sup>+</sup> T cells in transgenic mice expressing influenza virus protein hemagglutinin in the hypocretin cells.<sup>12,13</sup> In some cases, narcolepsy type 2 may be caused by a less extensive loss of these neurons, but this disorder is probably heterogeneous, and knowledge about its pathophysiology is still limited.

An autoimmune process probably mediates the selective destruction of hypothalamic hypocretin neurons in narcolepsy type 1. This hypothesis is supported by many epidemiologic and clinical findings: rare family cases, frequent discordance in monozygotic twins, young and bimodal age at onset, and a strong association with the 2009 H1N1 influenza pandemic and its vaccine (**Case 3-1**) and with streptococcal infections. However, no specific antibodies against hypocretin neurons have yet been discovered, possibly because of very small amounts of antibodies or due to a specific T-cell activation. Genetic background is of major importance, as more than 98% of patients with narcolepsy type 1 carry the HLA class II HLA-DQB1\*0602 allele,<sup>14</sup> compared to only 12% to 30% of the general population. More recently, the role of HLA class I<sup>15</sup> and other immune gene variants, such as the purinergic receptor *P2RY11* and T-cell receptor alpha locus *TRA*, was revealed.

Hypocretin neurons are normally active during wakefulness and function to stimulate other neurons in the cerebral cortex, basal forebrain, brainstem, and hypothalamus, producing norepinephrine, dopamine, serotonin, and histamine, which allow the maintenance of wakefulness through the day.<sup>16</sup> Hypocretin neurons also increase activity in the lateral pontine tegmentum that suppresses REM

sleep and project to brain regions that regulate metabolism, motivated behaviors such as reward seeking, and the autonomic system. In narcolepsy, the loss of hypocretin signaling results in excessive daytime sleepiness, dysregulation of REM sleep, and obesity in many patients, but with a large intervariability in symptom frequency and intensity. During cataplexy, positive emotions relayed through the amygdala and medial prefrontal cortex probably activate circuits in the dorsal pons responsible for muscle weakness in the absence of hypocretin, including the sublaterodorsal nucleus.

## Diagnosis

In *ICSD-3*,<sup>1</sup> narcolepsy type 1 is defined as the presence of excessive daytime sleepiness for more than 3 months, associated with either (1) the presence of cataplexy, a mean sleep latency of 8 minutes or fewer on the multiple sleep latency test, and at least two sleep-onset REM periods during the multiple sleep latency test or polysomnography or (2) a hypocretin-1 level of 110 pg/mL or less in the CSF, which is a highly specific biological measure.

Narcolepsy type 2 is defined by the presence of excessive daytime sleepiness without cataplexy for longer than 3 months, with a mean sleep latency of 8 minutes or fewer on the multiple sleep latency test, at least 2 sleep-onset REM periods on the multiple sleep latency test or polysomnography, and a hypocretin-1 level of higher than 110 pg/mL, if measured. Excessive daytime sleepiness must not be better explained by another cause, such as sleep deprivation, obstructive sleep apnea syndrome, circadian rhythm disorders, or the effect of a medication or substance abuse. If cataplexy appears over time, or if a hypocretin-1 measurement of 110 pg/mL or less is found, the condition is reclassified as narcolepsy type 1.

## KEY POINTS

- The etiology of narcolepsy type 1 is not yet completely understood, but an autoimmune process is highly suspected, with a role of genetic (human leukocyte antigen DQB1\*0602 allele) and environmental (influenza A vaccination) factors.
- Narcolepsy type 1 is associated with a wide range of sleep abnormalities and metabolic, cardiovascular, autonomic, and psychiatric consequences, in which the direct role of the hypocretin system remains to be defined.

**KEY POINT**

■ Treatment of narcolepsy is symptomatic and focuses on improving sleepiness and cataplexy.

Narcolepsy type 1 is a chronic disease requiring lifelong treatment, as the destruction of hypocretin neurons is irreversible. On the other hand, narcolepsy type 2 has a variable phenotype and evolution, with improvement or even disappearance of the symptoms, the development of cataplexy, or a change in the phenotype to idiopathic hypersomnia (refer to the section on clinical features of idiopathic hypersomnia).

**Treatment Options**

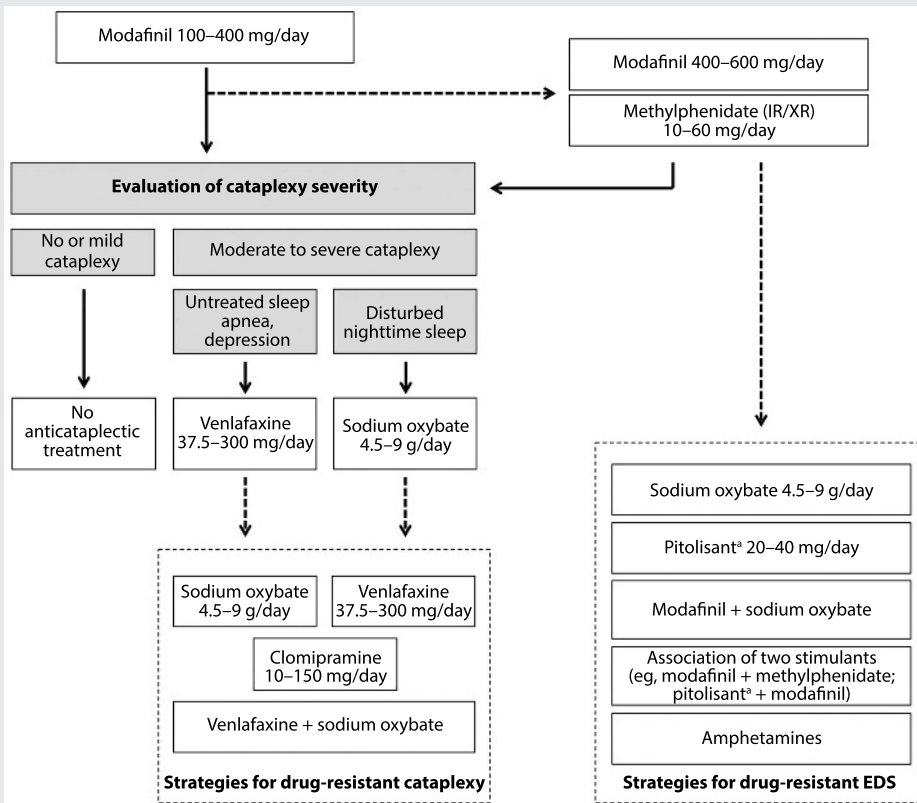
Narcolepsy treatment is symptomatic and varies from a single drug targeting several symptoms to multiple drugs to address different symptoms.<sup>17</sup> Recent clinical trials and practice guidelines have confirmed that stimulants such as modafinil, armodafinil, or sodium oxybate (as first line); methylphenidate and pitolisant (as second line [pitolisant is currently only available in Europe]); and amphetamines (as third line) are appropriate medications for excessive daytime sleepiness.<sup>17</sup> Women of childbearing potential receiving modafinil or armodafinil should be forewarned about the potential for reduced efficacy of hormonal contraceptives while receiving these drugs, which induce hepatic cytochrome systems and reduce serum concentrations of estrogenic drugs, possibly leading to increased risk of contraceptive failure and unintended pregnancy. Use of barrier contraceptives, increased dose of hormonal contraceptives, or an alternative noninducing psychostimulant such as methylphenidate should be considered. Typical psychostimulant adverse effects include tremor, palpitations, and jitteriness. Patients receiving psychostimulants should also be instructed to carefully monitor their blood pressure to avoid the development of hypertension, and those receiving methylphenidate or

amphetamines should have ECG monitoring to evaluate for QTc prolongation when target dosages are reached.

Sodium oxybate is the only medication approved for both sleepiness and cataplexy in adults. Specific anti-cataplectic treatment should depend on the severity of this symptom, as mild cataplexy frequently improves with increased alertness following the initiation of wake-promoting therapies. Antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]) are commonly used for cataplexy based on expert consensus since no controlled trial evidence exists for this use. An algorithm for the management of the main symptoms of narcolepsy type 1 is presented in **Figure 3-1**. A list of common comorbidities and signs associated with narcolepsy type 1 and strategies for managing them are presented in **Table 3-2**.

Medications and guidelines for excessive daytime sleepiness in narcolepsy type 2 should be the same as for narcolepsy type 1. However, the treatment and phenotype should be regularly reassessed because of the variability of the narcolepsy type 2 phenotype and the possible evolution toward a normal condition.

Good sleep hygiene is also recommended, including avoiding sleep deprivation, maintaining a regular nighttime sleep schedule, and scheduling short naps. As most of the symptoms in narcolepsy type 1 are directly explained by hypocretin deficiency, hypocretin replacement could be an ideal specific therapy for narcolepsy type 1, but the development of a clinical formulation is limited by the impermeability of the blood-brain barrier to this large neuropeptide. Immune-based therapies, administered very close to disease onset, could modify the natural history and the clinical course of the disease, although



**FIGURE 3-1** Decision tree for managing excessive daytime sleepiness and cataplexy in narcolepsy type 1.

EDS = excessive daytime sleepiness; IR = immediate release; XR = extended release.

\* Pitolisant is currently only available in European Union countries.

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**TABLE 3-2** Management of Symptoms and Comorbidities in Narcolepsy Type 1<sup>a</sup>

Symptoms and Comorbidities	Management Strategies
Disturbed nighttime sleep	Sodium oxybate; regular sleep-wake schedule; avoid long naps late in the day; avoid psychostimulant intake during the afternoon; hypnotic medications may be considered
Sleep paralysis/hypnagogic and hypnopompic hallucinations	Sodium oxybate, antidepressants (eg, venlafaxine, fluoxetine); provide information, education, and reassurance
Unpleasant dreams/recurrent nightmares	Antidepressants; cognitive-behavioral therapy

*Continued on page 996*

**TABLE 3-2** Management of Symptoms and Comorbidities in Narcolepsy Type 1<sup>a</sup> *Continued from page 995*

Symptoms and Comorbidities	Management Strategies
<b>Neuropsychiatric disorders</b>	
Mood disorders/ anxiety disorders	Antidepressants; psychotherapy; avoid sodium oxybate if possible
Psychotic symptoms	Consider antipsychotic drugs such as aripiprazole; use psychostimulants with caution (except pitolisant <sup>b</sup> , which is a new psychostimulant without dopaminergic activity, thus without any deleterious impact suspected on positive psychotic symptoms)
Attention deficit hyperactivity disorder	Methylphenidate; psychotherapy
<b>Cardiovascular and metabolic disorders</b>	
Overweight/obesity	Sodium oxybate, most psychostimulants; dietary measures and exercise; avoid tricyclic antidepressants; prescribe antidepressants at minimal doses
Type 2 diabetes mellitus	Sodium oxybate, most psychostimulants; dietary measures and exercise; avoid tricyclic antidepressants; prescribe antidepressants at minimal doses
Obstructive sleep apnea syndrome	Continuous positive airway pressure; loss of weight; use sodium oxybate with caution <sup>c</sup>
Cardiovascular diseases (eg, cardiac rhythm abnormalities, palpitations)	Use all psychostimulants with caution (except pitolisant <sup>b</sup> , which is a good alternative in case of cardiovascular disorder)
<b>Other sleep disorders</b>	
Rapid eye movement (REM) sleep behavior disorder (RBD)	Melatonin, clonazepam, possibly sodium oxybate (if already indicated for cataplexy or excessive daytime sleepiness symptoms); antidepressants can worsen RBD and should be avoided or given at minimal doses if RBD is severe
Non-REM–related parasomnias (eg, sleepwalking, sleep terrors, enuresis)	Clonazepam; avoid sodium oxybate when possible
Restless legs syndrome (RLS), periodic leg movements	Sodium oxybate and antidepressants may worsen RLS and periodic leg movements and should be avoided or given at minimal doses if RLS is severe; check ferritin/transferrin saturation percentage to exclude iron deficiency; sometimes specific treatment of RLS is required

<sup>a</sup> Managing excessive daytime sleepiness and cataplexy should be a clinician's priority because they are often the most severe and disabling symptoms. This table provides management strategies for other symptoms and comorbidities usually associated with narcolepsy type 1. The medications used for excessive daytime sleepiness and cataplexy can improve some of those comorbidities, but the same medications can also worsen others. In these conditions, the drugs are not necessarily contraindicated, but should be used with caution, at minimal doses if required, and benefit-risk balance should be well assessed.

<sup>b</sup> Pitolisant is currently only available in European Union countries.

<sup>c</sup> Note that sodium oxybate has a sedative effect along with a theoretic risk of hypoventilation, but can also reduce weight and thus improve obstructive sleep apnea syndrome.

no current evidence exists to guide such an approach, and future controlled trials will be necessary to determine if immunomodulatory approaches could impact the natural history or clinical symptom burden in narcolepsy. Other new psychostimulants are expected to emerge within the next few years: JZP-110 (a phenylalanine derivative with dopaminergic and noradrenergic activity), longer-acting formulations of sodium oxybate, and a combination of modafinil with connexin inhibitors are currently in development.

A recent valid, reliable, and informative narcolepsy-specific instrument referred to as the Narcolepsy Severity Scale was developed to monitor symptom severity and changes after treatment.<sup>18</sup> Physicians can use this brief scale to assess narcolepsy type 1 symptom frequency, severity, and consequences; to detect changes in symptoms after treatment; and to provide guidance on whether treatment goals are met.

Clinical evidence shows that medications approved for adults are also effective in children,<sup>19</sup> but specific guidelines are still lacking. Several multicenter clinical trials are currently ongoing in the pediatric narcolepsy type 1 population.

All patients with narcolepsy and central hypersomnias with uncontrolled sleepiness should be warned about the possible risks of driving while impaired and instructed not to drive when drowsy. Sleepiness and vigilance under medication can be objectively measured with the maintenance of wakefulness test, which may be important in assessing the capacity to drive. In some cases, medical restriction of driving privileges may need to be considered, depending on the severity of excessive daytime sleepiness symptoms and previous reported history of near misses or motor vehicle collisions. For more information, refer to the article “Driving

Safety and Fitness to Drive in Sleep Disorders” by Jon Tippin, MD, FAAN, FAASM, and Mark Eric Dyken, MD, FAHA, FAASM, FANA,<sup>20</sup> in this issue of *Continuum*.

## IDIOPATHIC HYPERSOMNIA

Idiopathic hypersomnia is another rare central hypersomnia that has been identified more recently than narcolepsy type 1 and is probably even more rare, although no epidemiologic studies are available to date. The sex ratio seems to be in favor of women, and the age at onset of the disease is often after puberty but under 30 years old.<sup>21</sup>

## Clinical Features

Two idiopathic hypersomnia phenotypes have been described, one with prolonged nighttime sleep and the other without long nighttime sleep.<sup>22,23</sup> A pervasive excessive daytime sleepiness characterizes the first form, with a prolonged nocturnal sleep duration of more than 10 or 11 hours and good-quality nighttime sleep with few arousals. It is associated with difficulties in waking up in the morning, a symptom known as sleep inertia and defined by reduced vigilance during the minutes or hours following arousal in the morning or from daytime naps. Patients describe an excessive time to be fully operational and sometimes describe mental confusion.<sup>24</sup> Daytime naps are typically long, lasting up to several hours, and unrefreshing in quality. In the form of idiopathic hypersomnia called *idiopathic hypersomnia without long sleep time*, the nighttime sleep is of normal quantity and quality (more than 6 hours and fewer than 10 hours), without sleep inertia, and sleep during the daytime is short and refreshing. These two phenotypes of idiopathic hypersomnia sometimes overlap and are pooled as one

## KEY POINTS

- All patients with narcolepsy and central hypersomnias with uncontrolled sleepiness should be warned about the possible risks of driving while impaired and instructed not to drive when drowsy.
- Idiopathic hypersomnia is another rare central hypersomnia that has been identified more recently than narcolepsy type 1 and is probably even more rare.



**KEY POINT**

■ The etiology of idiopathic hypersomnia is still unknown, but homeostatic and circadian disturbances and a deficient arousal system have been suggested.

diagnosis in *ICSD-3*. Hypnagogic hallucinations and sleep paralysis are rare in idiopathic hypersomnia, and the workup must exclude the presence of cataplexy.

Idiopathic hypersomnia is a disorder with frequent phenotype variation, and a continuum may exist between the forms with and without long sleep time and narcolepsy type 2. Indeed, the presence of one sleep-onset REM period is the only different diagnostic criterion between narcolepsy type 2 and idiopathic hypersomnia, and this electrophysiologic biomarker is unstable and sometimes not reproducible. The symptoms of idiopathic hypersomnia can be severe and chronic, but it is also important to inform patients that idiopathic hypersomnia symptoms disappear over time in up to 50% of patients. Clinicians must regularly reevaluate the presence

and severity of symptoms, the diagnosis, and management (**Case 3-2**).

**Pathophysiology**

Idiopathic hypersomnia is probably a heterogeneous disease, and this could explain why its physiopathology remains largely unknown. No biomarker specific to idiopathic hypersomnia has yet been identified. A circadian or homeostatic dysregulation or a disturbance in brain arousal systems is suspected. A dysfunction of the  $\gamma$ -aminobutyric acid–mediated (GABA-ergic) signaling pathway was reported in 2012,<sup>25</sup> but no active component in the CSF has been found and no difference with other central hypersomnias has been shown. Moreover, these results were not replicated in a 2016 study.<sup>26</sup> No genetic factor has yet been identified in idiopathic hypersomnia.

**Case 3-2**

A 25-year-old woman presented with a 1-year history of hypersomnolence, without mood disorders or any comorbid conditions. She slept an average of 11 hours at night and needed a 2-hour nap every afternoon. She lost her job because she was always late, as awakening in the morning and after the nap was extremely difficult, and she had major sleep inertia. Brain MRI was normal. Polysomnography followed by a multiple sleep latency test showed normal sleep at night, with high efficiency (95%) and a mean sleep latency of 7 minutes, without any sleep-onset rapid eye movement (REM) periods.

She was diagnosed with idiopathic hypersomnia. Modafinil was started but was not effective for her hypersomnolence and sleep inertia at a maximal dose of 600 mg/d. A second-line therapy, methylphenidate, was introduced; however, it was not well tolerated, with resultant irritability and palpitations. She was lost to follow-up but returned to the clinic 3 years later. She had stopped the medication during her pregnancy and felt no rebound of excessive daytime sleepiness. Polysomnography was again performed and showed normal mean sleep latency on the multiple sleep latency test (15 minutes). The psychostimulant did not need to be renewed.

**Comment.** This case illustrates the difficulty in managing hypersomnolence and sleep inertia symptoms in idiopathic hypersomnia and the variability of the idiopathic hypersomnia phenotype with possible evolution toward a normal condition, which is a relatively common phenomenon in clinical practice. Women of childbearing age must be informed that modafinil could decrease the efficiency of contraceptive agents, so another contraceptive method should be employed.

## Diagnosis

The diagnosis of idiopathic hypersomnia must be established according to *ICSD-3*,<sup>1</sup> with the presence of all of the following criteria: (1) excessive daytime sleepiness, irrepressible need to sleep, or daytime lapses into sleep for the past 3 months without cataplexy; (2) a mean sleep latency on the multiple sleep latency test of 8 or fewer minutes and/or a total sleep time on a continued 24-hour polysomnography recording of more than 11 hours, after correction of chronic sleep deprivation; (3) no more than one sleep-onset REM period on polysomnography and the multiple sleep latency test. In *ICSD-3*, wrist actigraphy and a sleep diary over 1 week preceding polysomnography can be used to demonstrate the prolonged sleep time and exclude insufficient nighttime sleep duration. It is important to confirm the persistence of excessive daytime sleepiness after a period of sleep extension, and excessive daytime sleepiness must not be explained more clearly by another sleep disorder (such as circadian rhythm disturbances), endocrine or neurologic disorders (in particular, vascular, tumor-associated, infectious, or neurodegenerative lesions affecting the arousal circuits), psychiatric disorders, or use of drugs or sedating medications.

The most challenging differential diagnosis is probably major depressive disorder, as hypersomnolence and fatigue can be among the first or main symptoms in mood disorders. Furthermore, patients with idiopathic hypersomnia can present with depressive symptoms, probably because of disease-related impairment in function and quality of life. When a patient presents with depressive symptoms and a suspicion of idiopathic hypersomnia, the physician should carefully evaluate

the date of onset of every symptom, the evolution of excessive daytime sleepiness depending on mood, and the effect of the treatment of depressive symptoms on excessive daytime sleepiness. An evaluation by a psychiatrist or a therapeutic trial with antidepressants is sometimes needed before further investigations are carried out.

## Treatment Options

Modafinil is effective in the treatment of excessive daytime sleepiness in idiopathic hypersomnia and should be the first-line therapeutic option.<sup>27,28</sup> Methylphenidate is the second-line treatment,<sup>29</sup> and amphetamines or pitolisant (currently available only in European Union countries) can be proposed when idiopathic hypersomnia is resistant to modafinil and methylphenidate or if those medications are not well tolerated. Some studies have suggested that sodium oxybate could be effective for excessive daytime sleepiness and sleep inertia in idiopathic hypersomnia.<sup>30</sup> However, systematic studies of the use of sodium oxybate in idiopathic hypersomnia with a strong methodology are lacking. Dextroamphetamine can also be used in the case of treatment-resistant idiopathic hypersomnia.<sup>29</sup> Sleep inertia is difficult to manage, and available medications are still unsatisfactory to reduce that symptom. Planned naps are seldom indicated in idiopathic hypersomnia, as they are often of long duration and not refreshing. It is also important to counsel patients with idiopathic hypersomnia about planning appropriate school and university schedules that allow for therapeutic napping, and, if possible, to plan for career work that is active and engaging. Clinicians must also frequently advocate for appropriate school and workplace accommodation for patients with

## KEY POINTS

- The differential diagnosis of idiopathic hypersomnia must exclude chronic insufficient sleep syndrome, especially in long sleepers. The diagnosis of idiopathic hypersomnia requires the exclusion of other sleep, medical, and psychiatric comorbidities.
- Idiopathic hypersomnia is most frequently managed with psychostimulants, but evidence for their use in idiopathic hypersomnia remains poor, and medications are usually unsatisfactory in managing sleep inertia.



**KEY POINTS**

- Kleine-Levin syndrome is a recurrent hypersomnia associated with behavioral, psychological, and cognitive disturbances during episodes, with strictly normal sleep and functioning between episodes.
- Diagnostic criteria for Kleine-Levin syndrome are only clinically defined, and no reliable biomarker has yet been identified.

idiopathic hypersomnia, and avoiding early morning starts to better enable adequate sleep can be beneficial.

**KLEINE-LEVIN SYNDROME**

Kleine-Levin syndrome is a recurrent hypersomnia with an estimated prevalence of about 1 to 2 per million that affects young people during the second decade of life, especially young men (male to female ratio of 2:1).

**Clinical Features**

Kleine-Levin syndrome is characterized by relapsing-remitting episodes of severe hypersomnolence associated with behavioral and psychiatric disturbances, cognitive abnormalities, and hyperphagia or hypersexuality.<sup>31,32</sup>

The median duration of an episode is 10 days, recurring every 1 to 12 months. A triggering factor, such as infection or alcohol intake, is often reported. During episodes, patients can sleep for 16 to 20 hours per 24 hours and are irritable if prevented from doing so. During their wake period, they are apathetic, confused, and slow in speaking and may have variable anterograde amnesia. Derealization is also typical (dreamlike and altered perception of the environment) as are hallucinations and delusions. Sleep, cognition, mood, eating, and sexual behavior are usually normal between episodes.

**Pathophysiology**

Kleine-Levin syndrome is likely a heterogeneous disease, with the underlying pathophysiology remaining unclear; however, some studies suggest recurrent primary hypothalamic dysfunction mediated by immune mechanisms.<sup>33</sup> Postmortem examinations have revealed inflammation of the hypothalamus, amygdala, temporal lobes, and thalamus. During episodes, functional brain imaging is abnormal, with metabolic changes in several brain re-

gions (thalamus, hypothalamus, mesial temporal and frontal lobes).<sup>34,35</sup> The young age at onset and triggering factors, such as infection, suggest a possible autoimmune process. The hypothesized etiology that is most likely is a recurrent, transient, multifocal encephalopathy.<sup>33</sup>

**Diagnosis**

Diagnostic criteria for Kleine-Levin syndrome are only clinically defined, without any reliable biomarker yet identified. According to *ICSD-3*,<sup>1</sup> Kleine-Levin syndrome is diagnosed by the presence of all the following criteria:

- The patient experiences at least two recurrent episodes of excessive daytime sleepiness lasting 2 days to 5 weeks that recur usually more than once a year and at least every 18 months.
- Between episodes, mood, alertness, cognitive function, and behavior are strictly normal.
- During episodes, the patient has at least one of the following symptoms: cognitive dysfunction, altered perception, eating disorder (anorexia or hyperphagia), or disinhibited behavior (such as hypersexuality).
- The symptoms are not explained by another sleep disorder, other medical or psychiatric disorder (especially bipolar disease), or use of substance or medication.

If performed, 24-hour polysomnography shows prolonged total sleep time during episodes, and CSF cytology and protein are normal.<sup>36</sup> However, some studies showed that intraepisodic levels of CSF hypocretin-1 can be lower than interepisodic levels.<sup>36</sup>

**Treatment Options**

No medication has clearly demonstrated its efficacy in the treatment of

Kleine-Levin syndrome, and most practices are based on case reports, case series, or open-label trials.<sup>31</sup> Placebo-controlled trials are extremely difficult to perform because of the rarity of the disease. Symptomatic treatments are based on stimulants such as modafinil but can induce paradoxical agitation; they are of poor efficacy since cognitive and behavioral problems will remain despite improvement in the vigilance state. Moreover, the spontaneous disappearance of symptoms after a few days of evolution leads to difficulties in proper evaluation of the potential benefit of these drugs. Prophylactic treatments based on mood stabilizers such as lithium<sup>37</sup> or anti-epileptic drugs (valproic acid, carbamazepine, phenytoin, gabapentin, and lamotrigine)<sup>38</sup> may be prescribed and have reportedly been effective to decrease the frequency and duration of episodes. The prognosis for Kleine-Levin syndrome is generally good, with a spontaneous resolution of the symptoms after a median of 14 years; therefore, routine pharmacologic management is sometimes not needed, especially when episodes are rare or lack major social impact. Patients should be allowed to rest in a safe and stress-free environment during an episode.

## OTHER CENTRAL HYPERSOMNIAS

In *ICSD-3*, three other central disorders of hypersomnolence are also defined: hypersomnia due to a medical disorder, hypersomnia due to a medication or substance or to stimulant withdrawal, and hypersomnia associated with a psychiatric disorder.<sup>1</sup>

In hypersomnia due to a medical disorder, the mean sleep latency on the multiple sleep latency test is fewer than 8 minutes, and excessive daytime sleepiness occurs as a consequence of a medical or neurologic condition.

Some examples include brain tumors, residual excessive daytime sleepiness in patients with adequately treated sleep apnea, genetic disorders such as Niemann-Pick disease type C, or hypersomnolence secondary to Parkinson disease. If criteria for narcolepsy are fulfilled, the diagnosis is narcolepsy type 1 or narcolepsy type 2 due to a medical condition. Indeed, on rare occasions, narcolepsy can be caused by a broad injury of the hypothalamus or of the projections of the hypocretin neurons as a consequence of a cerebral lesion (tumor, stroke, sarcoidosis, demyelination) or paraneoplastic disorder.<sup>39</sup> Patients with myotonic dystrophy have a narcolepsy type 2 phenotype in 30% of cases.<sup>40</sup>

The diagnosis of hypersomnia due to a medication or a substance or to stimulant withdrawal should be considered when daytime sleepiness occurs in the setting of current medication or substance abuse or withdrawal from a wake-promoting medication or substance. Indeed, the chronology of the onset of excessive daytime sleepiness needs to be compatible with such conditions of drug intake or withdrawal. Stimulant abuse and the excessive daytime sleepiness due to their withdrawal is more frequent among adolescents and young adults.

Hypersomnia associated with a psychiatric disorder is a complex entity and subject to controversy. The mean sleep latency on the multiple sleep latency test is fewer than 8 minutes, and the patient also presents with a psychiatric condition. Hypersomnolence is indeed frequent in the context of mood disorders; however, the sleep latency on multiple sleep latency test is often normal.<sup>41</sup> A challenge for sleep specialists and psychiatrists is to differentiate psychiatric hypersomnolence from a central hypersomnia disorder with comorbid psychiatric

## KEY POINTS

- The prognosis for Kleine-Levin syndrome is generally good, with a spontaneous resolution of the symptoms after a median of 14 years.
- Hypersomnia due to a medication or a substance, sleep deprivation, or a psychiatric disorder must always be considered in the differential diagnosis of narcolepsy type 2 and idiopathic hypersomnia.

symptoms. The current diagnostic tools seem to be limited in this combination of conditions, and further research is warranted.<sup>42</sup>

### DIFFERENTIAL DIAGNOSIS

The differential diagnoses of excessive daytime sleepiness are numerous, and the most important and correctable is likely insufficient sleep syndrome. The clinician must carefully establish patients' sleep time on weekdays and weekends by personal or collateral history, sleep logs, or, sometimes, actigraphy, if needed. Extension of total sleep time during holidays or sometimes even on weekends results in resolution of symptoms. In a normal variant known as a *long sleeper*, habitual sleep is reported as refreshing, with normal daytime functioning, when the subject is allowed to sleep at least 9 or 10 hours per night, yet such individuals often report sleepiness when they are relatively sleep deprived and sleep less than their sleep requirement of 9 or 10 hours or longer. Shift workers may also present with excessive daytime sleepiness, even mimicking a narcolepsy type 2 phenotype.<sup>43</sup> It is also important to rule out other sleep disorders, such as obstructive sleep apnea or periodic limb movement disorder, or circadian disorders (such as delayed sleep-wake phase disorder), which can be responsible for excessive daytime sleepiness.

### CONCLUSION

Central disorders of hypersomnolence are rare but disabling diseases, with a long delay before diagnosis, sometimes reaching several years (a median of 10 years for narcolepsy type 1).<sup>44</sup> The categorization is often difficult for sleep specialists, especially for hypersomnias outside the spectrum of narcolepsy type 1, as reliable bio-

markers have not yet been discovered. It is important for clinicians to recognize the manifestations of central hypersomnia and to accurately diagnose and efficiently manage excessive daytime sleepiness to maximize the patient's quality of life and daily school or work performance and to minimize the risk of accidents.

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# Restless Legs Syndrome and Sleep-Related Movement Disorders

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## ABSTRACT

**Purpose of Review:** This article provides an update on six sleep-related movement disorders: restless legs syndrome (RLS), periodic limb movement disorder, sleep-related leg cramps, bruxism, rhythmic movement disorder, and propriospinal myoclonus, with an emphasis on RLS.

**Recent Findings:** RLS is a common sensorimotor disorder that impairs quality of life. RLS is frequently comorbid to neurologic, psychiatric, vascular, and inflammatory diseases. Accumulating evidence implicates the pathophysiology of RLS as a state of dopamine dysfunction and iron deficiency that occurs on a background of genetic susceptibility conferred by 6 gene polymorphisms. Multiple treatments approved by the US Food and Drug Administration (FDA) are available. Dopamine agonists and  $\alpha 2\delta$  calcium channel ligands are considered first-line treatments, but these treatments have very different side effect profiles that should be taken into consideration.

**Summary:** Sleep-related movement disorders are frequently encountered in clinical practice. For some disorders, particularly RLS and periodic limb movement disorder, our understanding of biology, epidemiology, and treatment is advanced. For others, much work is needed to determine optimal treatment strategies.

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## INTRODUCTION

Sleep-related movement disorders primarily manifest during sleep or shortly before a person falls asleep. The *International Classification of Sleep Disorders, Third Edition (ICSD-3)* details six such disorders affecting adults,<sup>1</sup> all of which will be discussed in this article, with an emphasis on restless legs syndrome (RLS).

## RESTLESS LEGS SYNDROME

RLS, also known as Willis-Ekbom disease, is a common sensorimotor disorder that predominantly, but not exclusively, affects the legs. RLS may result in severe sleep disruption and impairs quality of life to a similar extent as other chronic diseases,<sup>2</sup> although

treatment improves quality of life.<sup>3</sup> RLS is diagnosed clinically via diagnostic criteria available from the International RLS Study Group,<sup>4</sup> the *ICSD-3*,<sup>1</sup> and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*.<sup>5</sup> The three classifications vary slightly, but all contain five core criteria, encapsulated with the mnemonic **URGED**<sup>6</sup>:

- Urge to move the legs, often accompanied by leg discomfort
- Rest worsens the urge to move
- Getting up and moving improves the urge
- Evening or night worsens symptoms
- Disorders that mimic RLS have been excluded

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### Unlabeled Use of Products/Investigational Use Disclosure:

Dr Trotti discusses the unlabeled/investigational use of benzodiazepines, botulinum toxin, clonazepam, and clonidine for the treatment of bruxism; of clonazepam for the treatment of hypnic myoclonus and rhythmic movement disorder; of carbamazepine, carisoprodol, diltiazem, gabapentin, lamotrigine, magnesium, oxcarbazepine, quinine, and verapamil for the treatment of leg cramps; of clonazepam and topiramate for the treatment of propriospinal myoclonus; and of gabapentin, iron (including ferrous carboxymaltose), opioids, and pregabalin for the treatment of restless legs syndrome.

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# KEY POINTS

- Diagnosis of restless legs syndrome requires five criteria: the urge to move the legs, worsening of symptoms with rest, worsening of symptoms in the evening or night, improvement of symptoms with movement, and symptoms that are not better explained by another condition.
- Supportive criteria for a diagnosis of restless legs syndrome are periodic limb movements, a positive family history, and response to dopaminergic therapy.
- Periodic limb movements of sleep are seen in 80% of patients with restless legs syndrome on a single sleep study, but are also common in people without restless legs syndrome.
- The prevalence of restless legs syndrome is highest in European populations (5% to 12%), followed by Asian populations (1% to 8%). Scant data from African countries suggest a prevalence of less than 1%.
- Iron deficiency, end-stage renal disease, and pregnancy are strongly associated with restless legs syndrome. Resolution of these conditions (ie, with iron replacement therapy, renal transplant, or delivery) often improves restless legs syndrome.

In particular, sleep-related leg cramps and positional discomfort (ie, needing to shift to a more comfortable position) can bear surface resemblance to RLS; common mimics are listed in **Table 4-1**.

Several supportive criteria, which are useful in cases with equivocal symptom description, include periodic limb movements of sleep (PLMS), first-degree relatives with RLS, and symptom improvement with a dopaminergic medication.<sup>4</sup> PLMS are repetitive limb movements that occur predominantly within the first several hours of sleep. Periodic limb movements may also occur during wakefulness prior to sleep onset or during wakefulness after sleep onset. PLMS cluster as at least four movements, which are separated by 5 to 90 seconds (**Table 4-2**).<sup>7</sup> Classically, they are described as a Babinski (triple flexion type) movement, but involved muscles and their activation sequences are variable between and within individuals.<sup>8,9</sup> PLMS most commonly affect the legs and are quantified during sleep studies using tibialis anterior surface EMG. PLMS are neither fully sensitive nor specific for an RLS diagnosis, and a

sleep study is not required for an RLS diagnosis. PLMS are seen on sleep studies in 80% of patients with RLS<sup>10</sup> and in more than one-fourth of the middle-aged European population.<sup>11</sup>

## Epidemiology

RLS has substantial regional variation in prevalence, which is highest in European populations (5% to 12%), intermediate in Asian countries (1% to 8%), and lowest in African countries, in which the fewest studies have been performed (less than 1%).<sup>12</sup> RLS is more common in women than in men, an effect driven by parity. Nulliparous women have a similar rate of RLS to men, but the prevalence of RLS in women increases with the number of prior pregnancies.<sup>13</sup>

Three conditions most strongly associated with RLS are pregnancy, iron deficiency, and end-stage renal disease. RLS symptoms very commonly appear during pregnancy, increase in prevalence and severity with each passing trimester, and resolve with delivery in most affected women.<sup>14</sup> RLS is present in 25% to 35% of patients with iron deficiency anemia.<sup>15</sup> RLS symptoms are also very common in patients with end-stage renal disease, in whom dialysis does not relieve symptoms but successful renal transplant does.<sup>16</sup>

RLS appears overrepresented in several neurologic disorders, including stroke, multiple sclerosis, and migraine.<sup>17,18</sup> In all but the latter, structural lesions related to the primary disease may cause RLS symptoms to manifest. However, an alternative hypothesis for the association with stroke may be that RLS increases the risk for vascular events, including stroke.<sup>19</sup>

Epidemiologic studies have also shown an association between RLS and mood disorders (eg, depression, anxiety, panic disorder), which is independent of antidepressant use.<sup>6</sup> This relationship might reflect a common

**TABLE 4-1 Common Mimics of Restless Legs Syndrome<sup>a</sup>**

- ▶ Akathisia
- ▶ Arthralgia
- ▶ Habitual foot tapping
- ▶ Myalgia
- ▶ Peripheral venous insufficiency, leg edema
- ▶ Positional discomfort
- ▶ Sleep-related leg cramps

<sup>a</sup> Data from Allen RP, et al, *Sleep Med.* [sleep-journal.com/article/S1389-9457\(14\)00190-7/abstract](http://sleep-journal.com/article/S1389-9457(14)00190-7/abstract).

**TABLE 4-2 Scoring Criteria for Periodic Limb Movements of Sleep<sup>a</sup>**

- ▶ Duration of movement between 0.5 seconds and 10 seconds
- ▶ Amplitude of movement at least 8  $\mu$ V above resting EMG amplitude
- ▶ At least four consecutive movements
- ▶ Minimum time of 5 seconds between onset of consecutive movements
- ▶ Maximum time of 90 seconds between onset of consecutive movements
- ▶ Movement does not occur within 0.5 seconds of a respiratory event

EMG = electromyography.

<sup>a</sup> Data from Iber C, et al, American Academy of Sleep Medicine.<sup>7</sup>

pathophysiologic substrate, or RLS might worsen mood through sleep disruption.<sup>6</sup> Treatment of RLS is beneficial for mood symptoms, albeit sometimes modestly.<sup>3,20,21</sup> Antidepressants also cause or worsen RLS in 9% of patients.<sup>22</sup> This effect is most pronounced with mirtazapine (28%), less so with duloxetine (5%), and is least pronounced with citalopram (2%).

An association between RLS and cardiovascular disease was first reported in 2001, with an adjusted odds ratio of 2.5 for heart problems in patients with RLS.<sup>23</sup> Subsequently, the majority (approximately 75%) of cross-sectional studies have confirmed associations between RLS or PLMS and cardiovascular disease or hypertension.<sup>24</sup> Prospective studies on this association have been mixed, suggesting quite different possible relationships, which include: (1) an increased risk of stroke or heart disease in those with RLS at baseline; (2) no increased risk of cardiovascular disease in those with RLS; and (3) an increased risk of incident RLS in those with cardiovascular disease risk factors at baseline.<sup>24</sup> Mechanistically, several pathways exist by which RLS could increase cardiovascular risk. PLMS present in the majority of patients with RLS and are accompanied by transient increases in heart rate and blood pressure<sup>25</sup>; these sympathetic surges are

similar to those seen in obstructive sleep apnea and may represent a cardiovascular risk factor. Alternatively, the sleep disruption or mood dysregulation seen in RLS may contribute to cardiovascular risk.<sup>26</sup> RLS treatment with rotigotine results in a greater decrease in nocturnal blood pressure elevations than placebo,<sup>27</sup> but it is presently unknown whether treatment of RLS or limb movements modifies long-term vascular risk.

RLS is also comorbid to numerous other diseases, leading to several distinct hypotheses. First, the majority (89%) of disorders linked to RLS have an inflammatory or immune basis, suggesting that RLS could be mediated by inflammation.<sup>28</sup> Second, RLS might be triggered by multimorbidity even in the presence of a relatively low genetic predisposition.<sup>15</sup>

### Pathophysiology and Genetics

RLS is strongly heritable, with approximately one-half of patients having at least one affected first-degree relative. Genome-wide association studies have to date identified single-nucleotide polymorphisms that confer risk for RLS within the genes *BTBD9*, *MEIS1*, *PTPRD*, *MAP2K5*, *SKOR1*, and *TOX3*.<sup>29–31</sup> Animal models of RLS based upon *BTBD9* have provided face validity for the importance of this variant,<sup>32</sup> and ongoing

### KEY POINTS

- Neurologic disorders associated with restless legs syndrome include stroke, multiple sclerosis, and migraine. Psychiatric disorders associated with restless legs syndrome include depression and anxiety.
- Cross-sectional studies suggest an association between restless legs syndrome and cardiovascular disease. Restless legs syndrome might cause cardiovascular disease through increases in sympathetic activity associated with periodic limb movements of sleep (as manifested by increases in heart rate and blood pressure). Other work suggests that multimorbidity itself might increase the risk of restless legs syndrome.
- Six loci associated with the genetic risk for restless legs syndrome have been identified through genome-wide association studies. The mechanistic relationship between these genes and restless legs syndrome is under investigation, but work to date implicates genetic alterations of dopamine and iron function.

# KEY POINTS

- Despite initial improvement in symptoms with dopaminergic treatment, the pathophysiology of restless legs syndrome is now suspected to reflect dopamine dysfunction rather than a hypodopaminergic state.
- Central nervous system iron deficiency is part of the restless legs syndrome pathophysiology in at least some patients, and it interacts with dopamine to exacerbate the dopamine dysfunction.
- Treatment of restless legs syndrome should include the discontinuation, if possible, of medications that exacerbate restless legs syndrome: antidepressants, antipsychotics, and metoclopramide.
- A serum iron panel should be checked in all patients diagnosed with restless legs syndrome or augmentation.

reverse-genetic approaches building on genome-wide association findings have begun to identify relationships between these genes and iron and dopamine metabolism, both implicated in RLS pathophysiology.<sup>33</sup>

A hypodopaminergic pathology has long been suspected in the pathophysiology of RLS based on the clinical observation that dopaminergic medications improve RLS.<sup>34</sup> However, dopamine deficiency has not been consistently demonstrated. More recently, a hyperdopaminergic state, superimposed upon the circadian changes in dopamine availability, has been postulated in the pathophysiology of RLS.<sup>35</sup>

The role of central nervous system iron deficiency in RLS is better established, although, at present, it is not clear if brain iron deficiency explains all or only some cases of RLS. Iron and dopamine are intertwined in the central nervous system; for example, iron is a necessary cofactor for dopamine production via tyrosine hydroxylase, and animals raised in the setting of iron deficiency have abnormally functioning dopamine transporters.<sup>36</sup> Thus, a prevailing hypothesis is that, at least in some patients, central iron deficiency results in a state of dopaminergic dysfunction that manifests as RLS.

## Treatment

A review of the patient's medication list is the first management step in RLS. Antipsychotics and other medications causing dopamine antagonism, such as metoclopramide, may be an occult cause of RLS. For patients with depression and RLS, changes in depression treatment may be helpful. Bupropion is often suggested as a first-line treatment for depression in patients with RLS based on its dopaminergic activity. A randomized controlled trial of bupropion for RLS did not demonstrate sustained superior-

ity over placebo, but did provide evidence that bupropion does not worsen RLS.<sup>37</sup>

Nonpharmacologic treatment of RLS may be helpful as monotherapy or adjunctive treatment. Lower body resistance and aerobic exercise decrease RLS severity.<sup>38</sup> A vibratory counterstimulation device cleared by the US Food and Drug Administration (FDA) has demonstrated benefit in almost one-half of patients with RLS (compared to 17% of those receiving sham treatment<sup>39</sup>), although challenges of insurance coverage have limited adoption in practice. Furthermore, the recent American Academy of Neurology (AAN) practice guideline for RLS notes weak evidence against use of vibratory counterstimulus devices for RLS symptoms but weak evidence for their use to improve sleep in patients with RLS (**Supplemental Digital Content 4-1**, [links.lww.com/CONT/A220](http://links.lww.com/CONT/A220)).

Because of the common co-occurrence of RLS and iron deficiency, clinical guidelines recommend checking an iron panel (ferritin, percent of transferrin saturation, total iron binding capacity, and iron) in all patients with RLS.<sup>40,41</sup> Several placebo-controlled trials of iron for the treatment of RLS have been performed with mixed results, which may reflect study heterogeneity (eg, oral versus IV iron, different iron preparations, baseline iron status). In meta-analysis, evidence is not sufficient to conclude that iron therapy is effective for treatment of RLS.<sup>42</sup> However, based on clinical practice experience, guidelines recommend replacing iron in patients with RLS with ferritin levels lower than 50 ng/mL to 75 ng/mL,<sup>41</sup> generally beginning with oral iron and proceeding to IV iron (particularly ferric carboxymaltose) if needed.

The FDA has approved four medications and cleared one device for the treatment of RLS (**Table 4-3**),

**TABLE 4-3 Interventions Approved or Cleared by the US Food and Drug Administration for Treatment of Restless Legs Syndrome**

►  **$\alpha 2\delta$  Calcium Channel Ligands**

Gabapentin enacarbil

► **Device**

Vibratory counterstimulus device

► **Dopamine Agonists**

Pramipexole

Ropinirole

Rotigotine

although several other medications are also supported by randomized controlled trials. In cases where symptoms are severe enough to warrant prescription pharmacotherapy, dopamine agonists and  $\alpha 2\delta$  calcium channel ligands are generally considered first-line treatments. Doses of dopamine agonists used for RLS treatment are much lower than typical doses in patients with Parkinson disease and are timed to be taken approximately 2 hours before typical symptom onset. The starting dose of ropinirole is 0.25 mg/d, then is titrated as follows: 0.25 mg for 2 days, then 0.5 mg for 5 days, then may increase by 0.5 mg increments every week until an effective or maximum dose is achieved, whichever comes first. Doses above 4 mg/d should be avoided in patients with RLS whenever possible.<sup>43</sup> The pramipexole starting dose is 0.125 mg/d, and it may be increased by 0.125 mg increments every 4 to 7 days until symptom control or maximum dose is reached. The maximum recommended RLS dose of pramipexole is 0.75 mg/d (although this is an expert consensus recommendation that differs

from the FDA labeling of 0.5 mg/d).<sup>43</sup> Rotigotine is the only dopamine agonist that is dosed via daily transdermal patch, which is initiated at 1 mg/d, and may be escalated to 2 mg/d or 3 mg/d in increments of 1 mg/d every week.

Common side effects of dopamine agonists include nausea and headache. Impulse control disorders have been reported in patients with RLS on dopamine agonists, so prescribers should educate patients about this side effect and regularly ask patients about this.<sup>40</sup> Augmentation, which is a treatment-induced worsening of RLS over time that follows an initial response to medication, is characterized by the geographic spread of RLS symptoms to the upper body or arms and earlier temporal onset of symptoms. Augmentation is a particularly problematic side effect seen with dopamine agonists. Augmentation may be identified using several key questions about timing and location of symptoms (Table 4-4). Although augmentation is frequent and problematic, optimal management is unknown. The International RLS Study Group has offered a variety of strategies for augmentation treatment, including removal of exacerbating factors (eg, sleep deprivation, medications); split dosing of medication if augmentation is mild; or changing from a dopamine agonist to an  $\alpha 2\delta$  calcium channel ligand, a longer-acting dopamine agonist, or an opiate.<sup>43</sup> A 10-day drug-free period has also been advocated, but may be challenging.<sup>43</sup> Patients experiencing augmentation should have iron levels rechecked with oral or IV iron repletion if ferritin values are at or below the 50 ng/mL to 75 ng/mL range (Case 4-1).

The  $\alpha 2\delta$  calcium channel ligands (gabapentin, pregabalin, and gabapentin enacarbil) are now considered first-line RLS treatment, in part because of growing recognition that dopaminergic augmentation is relatively common and

**KEY POINTS**

- First-line treatments of restless legs syndrome include  $\alpha 2\delta$  calcium channel ligands and dopamine agonists.
- Medication should be dosed 2 hours before typical onset of symptoms, not after symptoms have begun.



**TABLE 4-4 Clinical Screening Questions for Augmentation in Patients With Restless Legs Syndrome<sup>a</sup>**

- ▶ Do symptoms currently begin earlier in the day than they did before the medication was started?
- ▶ Are higher doses or an earlier timing of the medication needed to control restless legs syndrome compared to a previously effective dose or timing?
- ▶ Have symptoms become more intense since starting the medication?
- ▶ Have symptoms spread to previously unaffected body parts (such as the arms) since starting the medication?

<sup>a</sup> Data from Garcia-Borreguero D, et al, *Sleep Med*.<sup>43</sup> [sleep-journal.com/article/S1389-9457\(16\)00056-3/abstract](http://sleep-journal.com/article/S1389-9457(16)00056-3/abstract).

can greatly distress patients. Of these three medications, only gabapentin enacarbil is approved for RLS treatment. Gabapentin enacarbil is a gabapentin prodrug with different dosing than gabapentin, taken as a single dinner-time dose of 600 mg. Clinical trials have demonstrated efficacy for RLS with

### Case 4-1

A 72-year-old man presented for a second opinion regarding restless legs syndrome (RLS). His symptoms met the diagnostic criteria and had begun decades earlier. After gradual worsening of symptoms, their severity eventually reached the point that he had opted to start treatment 2 years ago. Initially, his symptoms had responded well to pramipexole 0.5 mg taken 2 hours before symptom onset at bedtime. Over the 2 months prior to presentation for a second opinion, his symptoms had become markedly worse, had spread to his arms, had begun as early as 2:00 PM, and had become much more intense. His primary care doctor added gabapentin 300 mg before bedtime, which he could not titrate further because it resulted in a worsened mood.

When he presented for the second opinion, his laboratory values demonstrated a ferritin level of 10 ng/mL, a transferrin percent saturation of 8%, total iron binding capacity of 500 mcg/dL, and iron of 35 mcg/dL. Initiation of oral iron therapy was advised, with a plan to change to IV iron if oral iron was not tolerated or was insufficient and with a consideration of changing from pramipexole to rotigotine. He reported gradual improvement in symptoms with oral iron therapy. His primary care doctor began an evaluation of iron deficiency.

**Comment.** In this case, augmentation is diagnosed based on the earlier onset of symptoms, the spread of symptoms to previously unaffected body parts, and the greater severity of symptoms, which occurred in the setting of a dopaminergic treatment that was initially beneficial. Treatment strategies for augmentation considered in this case include screening for and treating iron deficiency and changing to a longer-acting form of a dopamine agonist. If gabapentin had been well tolerated, increasing the dose and weaning pramipexole would have been another reasonable treatment strategy, as would have consideration of opioid therapy.

gabapentin (usual effective dose of 900 mg/d to 2400 mg/d, divided into 2 or 3 daily or nightly doses) and pregabalin (usual effective dose of 150 mg/d to 450 mg/d given nightly 2 hours before bedtime or ahead of habitual symptom onset; if a total dosage of more than 300 mg is needed, this should be divided into 2 separate doses).<sup>41</sup> Common side effects of  $\alpha 2\delta$  calcium channel ligands include somnolence, dizziness, and peripheral edema. In light of the comorbidity of RLS and mood disorders, the potential for worsening of depression or even suicidality with this family of medications should be kept in mind. Recently, a large prospective pregnancy registry study has also suggested that pregabalin may have teratogenic risk in women of childbearing potential.<sup>44</sup> A large trial randomly assigned patients with RLS to pregabalin (300 mg/d) or pramipexole (0.25 mg/d or 0.5 mg/d) and demonstrated that both pregabalin and pramipexole were effective in reducing RLS symptoms, but with a higher rate of augmentation with pramipexole.<sup>45</sup>

For patients refractory to other medications, opioids may be useful in select cases. Opioids have proven efficacy for RLS compared to placebo,<sup>46</sup> and clinical series suggest that serious opioid side effects may be relatively rare in this population.<sup>47</sup> However, the decision to use opioid medications must be made in the broader context of opioid risks and benefits. Recently released Centers for Disease Control and Prevention (CDC) guidelines for the use of opioids to treat chronic pain, while not specifically addressing RLS, may offer some guidance.<sup>48</sup>

## PERIODIC LIMB MOVEMENT DISORDER

PLMS are a frequent finding in adults undergoing polysomnography and are characterized by a periodically recurring

series of at last four consecutive limb movements lasting between 0.5 seconds and 10.0 seconds, with an intervening period between limb movements lasting between 5 seconds and 90 seconds (**Figure 4-1**). PLMS are present in most patients with RLS, but are not specific for an RLS diagnosis, and the presence of PLMS does not imply RLS. PLMS also frequently occur in patients with narcolepsy, Parkinson disease, idiopathic REM sleep behavior disorder, and diabetes mellitus, among others, and increase with age.<sup>11</sup> Distinct from the mere presence of PLMS on a sleep study, the syndrome of *periodic limb movement disorder* has been proposed to encompass both the presence of PLMS and a symptom of either insomnia or excessive daytime sleepiness, with the implication that treatment of the limb movements will result in improvement in insomnia or daytime sleepiness symptoms.<sup>1</sup> While occasional patients endorse symptom improvement with treatment of PLMS, the diagnosis of periodic limb movement disorder should be used judiciously, because it appears that, in most cases, the presence of PLMS is unrelated to insomnia or sleepiness, and treatment of PLMS has no clear symptomatic benefit. Whether treatment of PLMS will impact vascular health remains an unanswered question, thus the majority of observed PLMS remain untreated.

## SLEEP-RELATED LEG CRAMPS

Sleep-related leg cramps are perhaps the most ubiquitous sleep-related movement disorder, present occasionally in at least one-third of adults older than age 60 and in one-half of adults older than age 80.<sup>1</sup> Nocturnal leg cramps may arise from sleep or wakefulness and are distinguished from RLS by the presence of a painful cramp (ie, a charley horse) or sustained involuntary muscle contraction. When frequent leg

### KEY POINTS

- The term *periodic limb movement disorder* should be reserved for patients who have periodic limb movements of sleep that cause sleep disruption or daytime dysfunction.
- Sleep-related leg cramps are present at least occasionally in most older adults. Quinine is no longer recommended because of serious adverse events. Alternative treatment is not well tested, but might include leg stretches at bedtime and diltiazem.





**FIGURE 4-1** Periodic limb movements of sleep in a 54-year-old woman. Four consecutive 30-second epochs are shown, with periodic leg movements occurring approximately every 20 seconds and culminating in an arousal from sleep (arrow).

Courtesy of Erik K. St. Louis, MD, MS, FAAN, FAASM.

cramps are also prominent during wakefulness, especially when cramps are more diffuse and affect other muscles beyond the calves or feet, the possibility of an underlying comorbid neuromuscular disorder should be considered. When sleep-related leg cramps are present in isolation, work-up is rarely necessary. However, when daytime cramps occur, a thorough neuromuscular examination and investigations such as serum creatine kinase and nerve conduction studies and EMG should be considered when appropriate to exclude neuromuscular disorders that are frequently associated with prominent cramping, including cramp-fasciculation syndrome, peripheral neuropathy, motor neuron

disease, myotonic dystrophy, and inflammatory myositis.

Despite their commonality and associated sleep disruption, optimal treatment for leg cramps is not defined. A recent Cochrane Review found that quinine treatment of 200 mg/d to 500 mg/d reduces the number of cramps as well as the number of days in which cramps occur (low-quality evidence) and reduces cramp intensity (moderate-quality evidence), with a low incidence of serious adverse events with use up to 60 days.<sup>49</sup> However, the FDA has recommended that prescription quinine not be used for leg cramps because of the risk of cardiac arrhythmias and hematologic events. Tonic water, which contains a

smaller amount of quinine (40 mg/L to 80 mg/L; approximately 20 mg in an 8-ounce glass) has historically been recommended, but its efficacy and safety for this purpose has not been well studied. Medications that may contribute to cramps (long-acting  $\beta$ -agonists, potassium-sparing diuretics, and thiazide diuretics<sup>50</sup>) should be removed when possible. Interventions that have shown at least some reported benefit for leg cramps include leg stretches, diltiazem, and magnesium, although magnesium has been reported to be helpful specifically in women who are pregnant. Of these measures, stretching of the calves and hamstrings is the least invasive and therefore may be a reasonable first-line option.<sup>51</sup> Other proposed treatments for sleep-related leg cramps lacking a firm evidence basis include gabapentin, sodium channel blocking antiepileptic drugs (ie, carbamazepine, oxcarbazepine, lamotrigine), B vitamins, verapamil, and carisoprodol.<sup>50</sup>

### SLEEP-RELATED BRUXISM

Bruxism is the repetitive clenching or grinding of teeth. It may be present during sleep or wakefulness, but these two manifestations are generally considered two distinct entities with partial clinical overlap.<sup>1</sup> Sleep-related bruxism may come to clinical attention when the noise disturbs bed partners, when rhythmic masticatory muscle activity is seen during polysomnography, or because of possibly associated symptoms such as morning jaw muscle pain, fatigue, temporal headache, or dental wear. Bruxism may frequently coexist with obstructive sleep apnea. When daytime bruxism is also present, the possibility of comorbid associated anxiety disorders should also be sought.

Treatment of bruxism is typically accomplished via a dental appliance used during sleep. However, in cases

where bruxism results in morning facial pain or fatigue, a mouth guard alone may not be sufficient. Pharmacologic options for bruxism that is refractory to dental appliances alone may include clonazepam, botulinum toxin, or clonidine, but available data are limited.<sup>52</sup>

### SLEEP-RELATED RHYTHMIC MOVEMENT DISORDER

Rhythmic, stereotyped, nonepileptic, large-amplitude body movements may occur shortly before sleep onset and persist into sleep in some cases. The behaviors tend to repeat at a frequency between 0.5 Hz and 2 Hz. Common manifestations include body rocking, head banging, and head rolling. If these behaviors are disruptive to sleep, result in daytime dysfunction, or are potentially injurious, they are characterized as sleep-related rhythmic movement disorder.<sup>47</sup> Such rhythmic movements are ubiquitous in infants (present in up to 60% of infants at 9 months of age) but decrease with age (5% at 5 years of age), sometimes persisting into adulthood. Although these behaviors typically have been characterized as a method of self-soothing, children tend to be amnesic for the movements, and adults generally do not report a volitional component.<sup>1</sup> Successful treatment with clonazepam has been reported. Head banging behaviors may be violent and frequent, especially in some children and adults with psychomotor maldevelopment, and, in such cases, recommendation for protective head gear worn at bedtime should be considered to prevent injury.

### PHYSIOLOGIC (HYPNIC) MYOCLONUS

Sleep-wake transition (hypnic) myoclonus may be focal or axial, and while physiologic, occasionally becomes prominent enough for patients to seek clinical attention. Diagnosis is usually

#### KEY POINTS

- Sleep-related bruxism may be treated with a mouth guard to prevent dental wear. Pharmacologic therapy, if necessary, may be attempted with botulinum toxin, clonidine, or benzodiazepines.
- Sleep-related rhythmic movements are ubiquitous in infants but decrease in prevalence through childhood and adulthood. Treatment with benzodiazepines is proposed for cases in which treatment is needed (eg, injury or disruption), but is not yet substantiated by clinical trial evidence.

**KEY POINT**

■ Hypnic myoclonus is a generally benign phenomenon seen within the first hour of sleep and is typically treated by minimizing triggers such as caffeine and stress.

clear on clinical history, with reports of focal or multifocal/axial body jerks that occur at the sleep-wake transition, generally within the first hour of sleep, leading to arousal and sleep fragmentation. Addressing and correcting aggravating influences such as excessive caffeine use, physical or emotional stress, or comorbid anxiety or mental health disorders is usually effective, but a brief course of clonazepam (0.25 mg to 0.5 mg) at bedtime can be considered to help minimize arousals in severe cases.

**PROPRIOSPINAL MYOCLONUS**

Propriospinal myoclonus is a rare sleep-wake transition movement disorder that also may occur during wakefulness. Typical movements include axial “sit-up” or “jack knife” type movements that may variably extend to the limbs, especially the legs. Diagnosis requires video-EEG polysomnography or waking movement disorder laboratory studies employing axial and thoracic EMG electrodes to demonstrate initiation of the myoclonic jerks segmentally over the axial muscles prior to the characteristic spread to other segments. Treatment is frequently difficult, with clonazepam or topiramate most often recommended. Recent evidence suggests that propriospinal myoclonus may often be overdiagnosed or misdiagnosed, and that functional movement disorders may emulate these movements quite closely.

**CONCLUSION**

The sleep-related movement disorders are common, with age- and region-specific variations in prevalence, and may contribute to impaired quality of life, disrupted sleep, and pain or discomfort. RLS is associated with a variety of neurologic and psychiatric disorders, and growing evidence supports a relationship between RLS and vascular

disease. While treatment options for RLS are plentiful and well supported by clinical trials, treatment options for the remaining sleep-related movement disorders are more limited and based on lower-level evidence.

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# Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias

Birgit Högl, MD; Alex Iranzo, MD

## ABSTRACT

**Purpose of Review:** The most common rapid eye movement (REM) parasomnia encountered by neurologists is REM sleep behavior disorder (RBD), and nightmares are so frequent that every neurologist should be able to differentiate them from the dream enactment of RBD. Isolated sleep paralysis is relatively common and is often mistaken for other neurologic disorders. This article summarizes the current state of the art in the diagnosis of RBD, discusses the role of specific questionnaires and polysomnography in the diagnosis of RBD, and reviews recent studies on idiopathic RBD as an early feature of a synucleinopathy, secondary RBD, and its management. Recent diagnostic criteria and implications of nightmares and isolated sleep paralysis are also reviewed.

**Recent Findings:** Idiopathic RBD can now be considered as part of the prodromal stage of a synucleinopathy. Therefore, an accurate diagnosis is mandatory, and this implies detection of REM sleep without atonia. The polysomnography montage, including EMG of the submentalis and flexor digitorum superficialis muscles, provides a high sensitivity and specificity for the diagnosis. The exact diagnosis is important for patient counseling and for future neuroprotective trials.

**Summary:** REM parasomnias include RBD, sleep paralysis, and nightmares, which have distinct clinical characteristics and different implications regarding diagnostic procedures, management, and prognosis.

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## INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD), nightmares, and sleep paralysis are categorized among parasomnias occurring specifically during REM sleep. In the past few years, important advances in research into these disorders have enriched the field, particularly in RBD, which has been linked to neurodegeneration.

## RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

RBD has a low prevalence in young adults, but is a more frequent parasomnia among the elderly, with an estimated prevalence of probable RBD of up to 7.7%.<sup>1–3</sup> The recent interest in RBD by neurologists is because, beyond its classification as a parasomnia, it has been recognized to be an early form of a synuclein disease.



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**KEY POINT**

■ Although rapid eye movement sleep behavior disorder can be suspected by the patient's history, polysomnography is required for a definite diagnosis.

**Diagnostic Criteria**

The current diagnostic criteria for RBD were published in the 2014 *International Classification of Sleep Disorders, Third Edition (ICSD-3)* by the American Academy of Sleep Medicine (AASM) (Table 5-1).<sup>4</sup> These criteria require that sleep-related vocalizations or complex motor behaviors plus pathologically increased muscle tone during REM sleep on the polysomnogram (REM sleep without atonia) are present. Although RBD can be suspected by history, for a definite diagnosis of RBD, polysomnography is required.

While former *ICSD* criteria only required “excessive” submental or (upper or lower) limb EMG activity during polysomnography for the diagnosis of RBD, the current *ICSD-3* criteria list exact polysomnography measures for scoring guidelines and are established on evidence-based data for detecting REM sleep without atonia in the evaluation of RBD.<sup>5,6</sup>

Typical clinical characteristics of RBD include sleep-related complex motor behaviors and vocalizations that are associated with dreaming. Observers have the impression that apparent

dream enactment is occurring (the behaviors seem to mimic dream content). Dream content is often elaborate, typical for REM-sleep dreaming, in contrast to the more static imagery and ruminations of non-REM dreamlike experiences. In RBD, patients can be awakened easily and are usually quickly oriented. The vocalizations and behaviors show a very large intraindividual and interindividual variability in RBD. This can be of some clinical help to differentiate the dream enactment behaviors of RBD from the lower variability of vocalizations in somniloquy and non-REM parasomnia or behaviors observed with periodic leg movements or sleep-related epilepsy. If subjects are not awakened immediately after the RBD episode or do not wake up spontaneously because of injury during an episode, dream content is frequently no longer remembered. The easy ability for awakening and reorientation in idiopathic RBD can help to clinically differentiate RBD from non-REM parasomnias and nocturnal wandering in dementia.

Because REM sleep is more likely to occur and REM episodes last longer in later parts of the night, RBD episodes often occur in the second half of the

**TABLE 5-1** *International Classification of Sleep Disorders, Third Edition, Diagnostic Criteria for Rapid Eye Movement Sleep Behavior Disorder*<sup>a</sup>

**All criteria of the following must be met for a diagnosis of rapid eye movement (REM) sleep behavior disorder**

- A. Repeated episodes of sleep-related vocalization and/or complex motor behaviors
- B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep
- C. Polysomnographic recording demonstrates REM sleep without atonia
- D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use

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night (whereas non-REM sleep parasomnias often occur in the first hours of sleep).

## Clinical History Taking

Mild RBD probably often goes undiagnosed, as patients may be unaware of their nighttime behaviors or may ignore that dream-associated behaviors reflect a pathology that should be reported to their physician.<sup>7,8</sup> Specific history taking for RBD should include the bed partner whenever possible. Useful screening questions for a partner can help determine if the patient seems to “dream a lot” or if the partner can observe what their partner dreams about. If a partner is not available, questions to the patient should relate to whether they have been told about such behaviors or if injuries or falls out of bed have occurred during sleep (with or without remembered dreaming). Specific history taking is necessary because RBD symptoms are often not spontaneously reported,<sup>9</sup> and, specifically in idiopathic RBD, only patients with more severe symptoms tend to be sent to the sleep laboratory.<sup>10</sup>

A history of dream enactment behavior alone is insufficient to diagnose RBD, as this occurs frequently in the general population and may point to non-REM parasomnia (eg, somnambulism, sleep terrors, hypnagogic hallucinations), other sleep disorders where abnormal behaviors may occur (eg, nocturnal epilepsy, vigorous periodic limb movements, severe obstructive sleep apnea), or may be confused with nightmares or visual hallucinations.

## Polysomnographic Diagnosis

Clinical diagnosis is always required in RBD, in addition to confirmatory polysomnographic features, along with recorded dream enactment behavior or complex behavior, according to current

ICSD-3 diagnostic standards. In other words, polysomnographic features of REM sleep without atonia alone are not diagnostic of RBD.

Polysomnography is mandatory for a definite and reliable diagnosis of RBD because other conditions may mimic its symptoms. Standardized protocols and normative values exist for making an exact quantitative diagnosis of RBD. The hallmark of RBD is abnormally increased activity on the surface EMG of chin (mental and submental) and upper or lower extremity surface EMG recordings during REM sleep on polysomnography. Usually, this abnormally increased EMG activity is subdivided into tonic and phasic or *any* EMG activity. Tonic EMG activity is characterized by a longer-lasting increase in the tone of the EMG (lasting longer than one-half of a 30-second epoch). Phasic EMG activity is characterized by shorter, often twitchlike increases in EMG tone, lasting 0.1 to 5 seconds.<sup>11</sup> While tonic EMG activity is usually only found in the mental/submental EMG, phasic activity is present in mental/submental as well as extremity muscles. Although different pathophysiologic pathways are thought to underlie tonic and phasic EMG activity in RBD, the term *any* EMG activity has been introduced for clinical reasons of quantification.<sup>6</sup>

Early during the course of the development of polysomnographic methods for the evaluation of RBD, Mahowald and Schenck<sup>12</sup> suggested that arm EMG should be recorded to accurately diagnose RBD. Because some patients have RBD behaviors mostly in the arms, and because EMG activity and movements during REM sleep in leg muscles are less specific, it is highly recommended to perform an EMG recording from the upper extremities in combination with the chin EMG to diagnose RBD (**Supplemental Digital**

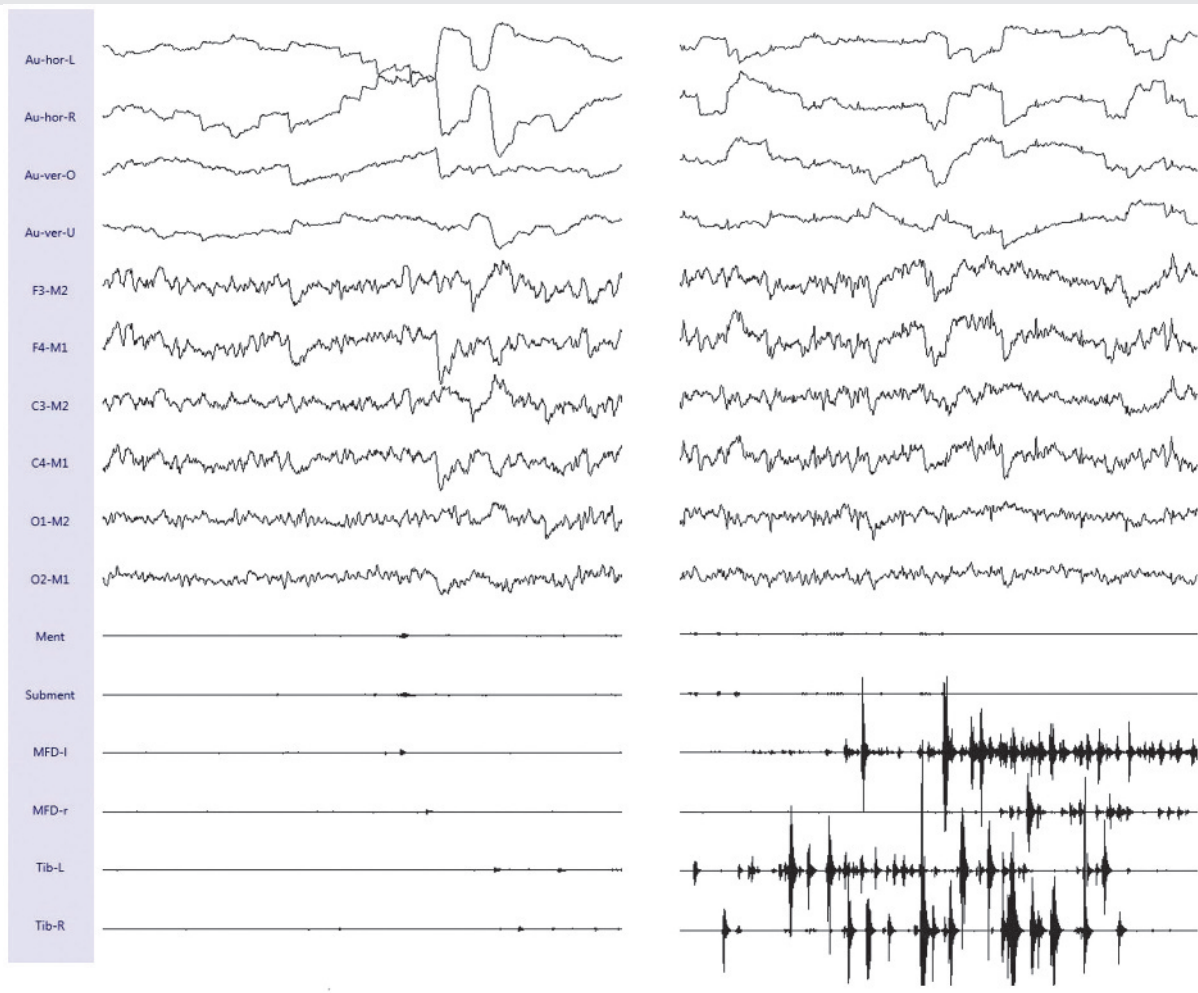
### KEY POINT

- Standardized protocols and normative values exist for making an exact quantitative diagnosis of rapid eye movement sleep behavior disorder.

**Content 5-1,** [links.lww.com/CONT/A221](https://links.lww.com/CONT/A221)) (Figure 5-1).<sup>13</sup>

Normative values for EMG activity that help to discriminate between RBD and controls have been published for 11 striated muscles (surface EMG),<sup>6</sup> and the most sensitive and specific, yet simple, EMG combination was of the mental/submental and flexor digitorum superficialis muscles in the upper limbs.<sup>6</sup> For accurate diagnosis of RBD, the polysomnography EMG

montage, therefore, should include the mentalis or submental muscle and both upper extremities (right and left flexor digitorum superficialis). Other published values refer to the chin alone, and recent work has demonstrated that a quantitative diagnosis of RBD with highly similar EMG values can also be feasible in polysomnography with tibialis anterior EMG recordings only, and even in split-night polysomnography including



**FIGURE 5-1** Examples from polysomnographic records (each panel is 10 seconds) from normal rapid eye movement (REM) sleep (left tracings) and REM sleep in a patient with REM sleep behavior disorder (RBD) (right tracings). The top four channels are horizontal and vertical electrooculography, the central six channels are EEG according to the American Academy of Sleep Medicine, and the bottom six channels represent mental and submental, left and right flexor digitorum superficialis, and left and right tibialis anterior muscles. Whereas in normal REM sleep, almost complete atonia is seen in all recorded muscle channels, in RBD, excessive phasic EMG activity is seen in both upper and lower extremity muscles. Note that in this epoch, the excessive muscle activity would not have been seen if chin EMG would have been recorded alone.

continuous positive airway pressure (CPAP) titration.<sup>14,15</sup> However, it is preferable, whenever possible, to have either full-night diagnostic or CPAP treatment studies rather than split-night studies, especially for research purposes.<sup>7</sup> The normative values require that any EMG activity (tonic, phasic, or other) in the combined recording of mentalis and right and left arm (flexor digitorum superficialis) during REM sleep should be at least 27% in 30-second epochs for RBD and 32% when a 3-second mini-epoch scoring approach is applied.<sup>16</sup>

Because visual quantification of increased EMG activity during REM sleep requires highly specific knowledge and is time consuming, several attempts have been made to develop computerized methods for automatic detection and quantification of EMG activity during REM sleep. A series of different approaches and techniques have been validated and published.<sup>17–20</sup> Some of them require separate software and analysis after polysomnography, while others can be run together with a regular polysomnographic analysis. Some rely on EMG activity analysis for the chin only.<sup>21,22</sup> Only one automatic analysis software designed to quantify EMG activity during REM sleep includes other additional muscles.<sup>19</sup>

Nevertheless, with either automated or visual scoring approaches, high technical quality of polysomnogram recordings and complete elimination of artifacts that can confound EMG activity analysis (such as snoring artifacts) are necessary, and a visual plausibility check of all calculated values with a cross-check of the original polysomnogram is necessary to ensure the quality of the diagnosis of RBD.<sup>23</sup>

One night of polysomnography recording is usually sufficient to make a diagnosis of RBD.<sup>24,25</sup> A second night is sometimes necessary in pa-

tients who do not have enough minutes of REM sleep during the first night of polysomnography or when REM sleep is markedly interrupted by apneas. In some clinical settings, the diagnosis of RBD may still have to be determined purely on clinical grounds, such as in developing regions with scarce resources, in large-scale epidemiologic studies where polysomnography is infeasible or unaffordable, or when REM sleep cannot be recorded or overall sleep architecture is so disturbed that recognition of REM sleep is impossible. Sleep architecture is often highly disturbed in advanced parkinsonism with underlying synucleinopathy, or sometimes in the setting of autoimmunity, as in the recently described IgLON5 autoimmunity syndrome,<sup>26,27</sup> which is now called anti-IgLON5 disease.<sup>28</sup> However, polysomnographic confirmation of RBD diagnosis should be considered the standard of practice.

### Questionnaires for Diagnosis

Because polysomnography is sometimes not readily available, several questionnaire-based instruments have been developed to screen for RBD, namely, the REM Sleep Behavior Disorder Screening Questionnaire, the REM Sleep Behavior Disorder Questionnaire Hong Kong,<sup>29</sup> the Mayo Sleep Questionnaire,<sup>30</sup> the Innsbruck REM Sleep Behavior Disorder Inventory,<sup>31</sup> and the International REM Sleep Behavior Disorder Study Group's REM Sleep Behavior Disorder Single-Question Screen.<sup>32</sup> All of these have been validated with a reasonable sensitivity and specificity in the context of the respective validation studies. Nevertheless, some recent work has shown that the sensitivity and specificity of diagnostic RBD questionnaires strongly depend on the settings<sup>33</sup>; false positives are very frequent if patients

### KEY POINT

■ For accurate polysomnographic diagnosis of rapid eye movement sleep behavior disorder, polysomnography should include an EMG montage using the mentalis or submental muscle and both upper extremities (right and left flexor digitorum superficialis).



**KEY POINTS**

- Patients with idiopathic rapid eye movement sleep behavior disorder have no motor or cognitive symptoms.
- Most individuals initially diagnosed with idiopathic rapid eye movement sleep behavior disorder are eventually diagnosed with Parkinson disease, dementia with Lewy bodies, and, less frequently, with multiple system atrophy.

have to complete the questionnaire themselves, and false negatives occur in patients who are unaware of their nocturnal behaviors.<sup>19</sup>

Therefore, it should be kept in mind that questionnaires are appropriate to make a diagnosis of probable RBD only, and their usefulness and outcomes rely on the intervention of a trained interviewer. For screening purposes, a multistep strategy including confirmatory polysomnography has therefore been recommended.<sup>34</sup>

Video-polysomnography is recommended to diagnose RBD, but in contrast to EMG, where published cutoff values exist, no cutoff values exist for video analysis.<sup>35</sup> Overall, the majority of motor events, even in severe RBD, are simple elementary movements,<sup>36</sup> and complex or violent behaviors are much more rare and initiated during REM sleep with rapid eye movements in the majority of patients (compared to REM sleep without rapid eye movements).<sup>37</sup> While minor jerks during REM sleep exist in the healthy population,<sup>35</sup> it has been suggested that apparently intentional behaviors (so-called REM sleep behavioral events) at night could indicate the future development of RBD in patients with early Parkinson disease (PD).<sup>38–40</sup>

**Idiopathic Rapid Eye Movement Sleep Behavior Disorder**

RBD can be divided into a primary (idiopathic form) or secondary form when the parasomnia is linked to a second condition or situation.

**Idiopathic rapid eye movement behavior disorder as an early feature of synucleinopathies.** Patients with idiopathic RBD have no daytime motor or cognitive symptoms. However, three lines of evidence indicate that idiopathic RBD is not an innocent sleep abnormality, but represents, at least in most older adult cases

presenting to sleep centers, the prodromal stage of a neurodegenerative disease characterized by neuronal cell loss and abnormal deposits of  $\alpha$ -synuclein in surviving cells. These diseases are termed synucleinopathies and include PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), with disease subtypes defined by specific motor, cognitive, or autonomic impairments at presentation. Longitudinal follow-up in patients with idiopathic RBD diagnosed in sleep centers shows that most individuals initially diagnosed with idiopathic RBD are eventually diagnosed with PD, DLB, and, less frequently, with MSA.

Schenck and colleagues<sup>41</sup> first showed that parkinsonism developed in 11 of 29 (38%) subjects with idiopathic RBD 4 years after the diagnosis of the sleep disorder and 13 years after the estimated onset of RBD symptoms. After 16 additional years, 21 (81%) patients from this cohort were diagnosed with PD, DLB, or MSA.<sup>42</sup> Iranzo and colleagues<sup>43</sup> found that 20 of 44 (45%) patients with idiopathic RBD developed a defined neurodegenerative syndrome after a mean follow-up of 5 years. Clinical diagnoses were PD ( $n = 9$ ), DLB ( $n = 6$ ), MSA ( $n = 1$ ), and mild cognitive impairment ( $n = 4$ ). After 7 years of additional follow-up, 36 (82%) developed PD ( $n = 16$ ), DLB ( $n = 14$ ), MSA ( $n = 1$ ), and mild cognitive impairment ( $n = 5$ ). The rates of phenoconversion from idiopathic RBD diagnosis were 35% at 5 years, 73% at 10 years, and 92.5% at 14 years.<sup>44</sup> Similar results have been found in a large international multicenter cohort involving 279 subjects.<sup>45</sup>

Overall, these observations indicate that RBD is usually not idiopathic per se, but perhaps most properly termed a cryptogenic disorder that

represents an early stage of PD and DLB before the clinical onset of overt parkinsonism and cognitive impairment. Interestingly, in the setting of RBD, the coexistence of mild cognitive impairment indicates the progression to dementia in less than 5 years.<sup>46</sup> Thus, in patients with RBD and comorbid cognitive impairment, the disease should not be considered idiopathic. Another important aspect is that the coexistence of RBD in subjects with cognitive impairment (either mild cognitive impairment or dementia) indicates that the underlying process is a synucleinopathy (DLB or PD) and not Alzheimer disease or frontotemporal dementia.

Patients with idiopathic RBD show often subtle subjective or objective clinical abnormalities that are typical features of the synucleinopathies. Patients with idiopathic RBD may show abnormalities typical of PD such as hyposmia, depression, constipation, and decreased

dopaminergic uptake in the putamen on functional imaging (**Case 5-1**).

Patients' perceived time of onset of RBD and nonmotor symptoms such as hyposmia, constipation, and depression are highly variable. Clinical examination may reveal facial akinesia, reduced arm swing, and other forms of subtle bradykinesia that still are not sufficient to disclose frank parkinsonism. Asymptomatic cognitive deficits in the executive, memory, and visuospatial domains are shown by neuropsychological tests, while electroencephalography may demonstrate subtle cortical slowing. Neuroimaging may show a number of abnormalities, including decreased metaiodobenzylguanidine uptake in cardiac scintigraphy; decreased putaminal dopamine uptake in dopamine transporter imaging; hyperechogenicity of the substantia nigra and hypoechogenicity on the brainstem raphe on transcranial sonography; loss of intensity in the substantia nigra and

#### KEY POINT

■ Patients with idiopathic rapid eye movement sleep behavior disorder show abnormalities typical of Parkinson disease such as hyposmia, depression, constipation, and decreased dopaminergic uptake in the putamen on functional imaging.

### Case 5-1

A 69-year-old man presented with a 4-year history of abnormal behaviors during sleep, which were described by his wife. Upon awakening, he would not recall these behaviors, which consisted of violent activities such as punching, kicking, knocking over the nightstand, and grabbing his wife by the neck. These behaviors were performed with his eyes closed and mainly during the second half of the night. If awakened during one of the episodes, he reported dreaming that unknown intruders were attacking him or chasing him. One night he jumped out of bed while dreaming that he was fighting against a lion. Another night he hit the wall and broke his right arm. He had no symptoms of insomnia, excessive daytime sleepiness, snoring, restless legs syndrome, or seizures. He reported no cognitive or motor problems. The patient had a history of depression and was treated with venlafaxine.

On examination, he had facial akinesia and reduced right arm swing, but limb bradykinesia, tremor, rigidity, and postural imbalance were absent. Video-polysomnography showed increased electromyographic activity during rapid eye movement (REM) sleep in all four limbs, but not in the mentalis, associated with jerks and raising the arms. Obstructive sleep apnea and periodic limb movements were absent. The patient was diagnosed with idiopathic REM sleep behavior disorder (idiopathic RBD), and clonazepam was started (1 mg at bedtime), which led to a dramatic decrease in dream-enacting behaviors.

*Continued on page 1024*



**KEY POINT**

■ Dysfunction in idiopathic rapid eye movement sleep behavior disorder is widespread and involves the olfactory system, the limbic system, the autonomic system, the nigrostriatal system, the hippocampus, and the cortex. These abnormalities do not occur in all subjects with idiopathic rapid eye movement sleep behavior disorder, and some individuals show only a few abnormalities, while others have many.

*Continued from page 1023*

During 5 years of follow-up, he developed constipation and loss of the sense of smell. Cognitive symptoms were still absent, but neuropsychological testing showed executive dysfunction. After 6 years of follow-up, he first reported motor slowness. Neurologic examination revealed shuffling gait, bilateral asymmetric bradykinesia, and rigidity, and he was diagnosed with Parkinson disease (PD). Dopamine transporter imaging showed decreased bilateral putaminal uptake. The patient started levodopa (750 mg/d), and motor examination showed improvement in bradykinesia and rigidity.

**Comment.** This case illustrates that idiopathic RBD may be the first feature of PD. It also shows that patients with idiopathic RBD have no motor or cognitive symptoms and may be unaware of their symptoms as reported by the bed partner; these symptoms, which may result in injuries, respond to clonazepam. Additionally, patients with idiopathic RBD have asymptomatic, usually covert prodromal historical features of PD (eg, depression, constipation, hyposmia), and their baseline examinations may show subtle parkinsonian signs and asymptomatic neuropsychological dysfunction. In this patient, the mentalis muscle was atonic on video-polysomnography, but diagnostic REM sleep atonia loss (REM sleep without atonia) was apparent only in the limbs, demonstrating the importance of recording EMG in the limbs, especially in the arms, where isolated REM atonia loss may be seen in the flexor digitorum superficialis muscles. Typically arising from idiopathic RBD, PD was characterized in this patient by the akinetic-rigid motor subtype that responded to conventional dopaminergic therapy.

locus coeruleus/subcoeruleus area on 3T MRI; abnormal metabolic network characterized by increased activity in the pons and hippocampus and decreased activity in occipital and temporal areas by positron emission tomography (PET); decreased fractional anisotropy and increased mean diffusivity in the midbrain and pontine nuclei that regulate REM in sleep diffusion-tensor imaging; and increased gray matter density in both hippocampi revealed by voxel-based morphometry.

These findings indicate that dysfunction in idiopathic RBD is widespread and involves the olfactory system, the limbic system, the autonomic system, the nigrostriatal system, the hippocampus, and the cortex. These abnormalities do not occur in all subjects with idiopathic RBD, and some individuals show only a few abnormalities, while others have many. This indicates that some patients with idiopathic RBD are close to

manifesting parkinsonism or cognitive decline, while others are not. Researchers have sought to establish which abnormalities identify those subjects with idiopathic RBD with a short-term risk for being diagnosed with PD, DLB, or MSA. They found that decreased dopaminergic putaminal uptake and hyposmia identify those subjects with idiopathic RBD who have an increased short-term risk (2.5 to 5 years) of being diagnosed with a synucleinopathy.<sup>47,48</sup> Patients with cortical electroencephalographic slowing tend to develop mild cognitive impairment and subsequent dementia. Hyperechogenicity of the substantia nigra alone and autonomic abnormalities do not seem to identify the risk for short-term conversion. Researchers have also evaluated if these abnormalities change with time, reflecting an active neurodegenerative process during the prodromal stage of the synucleinopathies. While dopamine

transporter imaging demonstrates progressive decline in putaminal uptake,<sup>49</sup> and tests show progressive cognitive deficits,<sup>50</sup> smell impairment, dysautonomic abnormalities, and the echogenic size of the substantia nigra by transcranial sonography remain unchanged with time. Abnormal deposits of phosphorylated  $\alpha$ -synuclein are detected in peripheral organs outside the brain in patients with idiopathic RBD.

The Sleep Innsbruck Barcelona (SINBAR) group<sup>51</sup> reported that colonic biopsies detected phosphorylated  $\alpha$ -synuclein aggregates in the submucosal nerve fibers or ganglia in four out of 17 patients with idiopathic RBD and in none of the 14 controls. In a second study, biopsy of the submandibular gland detected phosphorylated  $\alpha$ -synuclein deposits in greater than 85% of the subjects with idiopathic RBD, and in none of the controls, in whom glandular parenchyma was obtained by the procedure.<sup>52</sup>

## Secondary Rapid Eye Movement Sleep Behavior Disorder

Aside from the idiopathic form of RBD, the parasomnia can be found in association with other medical conditions or with the introduction of some medications and is referred to as secondary RBD.

**Diagnosis.** Confirmation with video-polysomnography is mandatory to establish the association between RBD and other conditions. RBD may be secondary to established neurodegenerative diseases (eg, PD, spinocerebellar ataxias), autoimmune diseases (eg, anti-IgLON5 disease, narcolepsy, paraneoplastic syndromes), focal brainstem lesions (eg, ischemic infarct, tumors), or induced by medications (eg, antidepressants).<sup>53</sup>

The link is established when the underlying condition impairs the brainstem (pons and medulla), limbic struc-

tures (amygdala), and pathways that modulate REM sleep atonia. Therefore, RBD is frequent in patients with neurodegenerative diseases (eg, PD, DLB, MSA) that affect these regions, but is rare in Alzheimer disease or frontotemporal dementia. For some conditions (eg, PD and MSA), RBD has been well characterized in a number of publications, while for other conditions (eg, Huntington disease, Machado-Joseph disease, PD with parkin2 mutations, myotonic dystrophy, Wilson disease), RBD has been reported in single or a few small case series involving small numbers of patients or in anecdotal reports (eg, attention deficit hyperactivity disorder). In some instances, RBD may be an important clinical feature, while in others it is not significant and is overlooked by other features (eg, dementia, parkinsonism, confusion, seizures). When RBD is associated with a neurodegenerative disease, the parasomnia may occur before or after the onset of the classic symptoms of the disease (eg, dementia, parkinsonism). In idiopathic PD, RBD is linked to a specific phenotype where male sex, the rigid-akinetic motor subtype, dysautonomia, and cognitive impairment predominate.<sup>54</sup> RBD occurs in the majority of patients with MSA, if not all, but only about one-half of them are aware of their vigorous dream-enacting behaviors. RBD in DLB (and in all dementias) should be distinguished from visual hallucinations resembling nightmares, and both confusional awakenings and episodes of nocturnal agitation can mimic the dream-enacting behaviors seen in RBD. Denervation of the amygdala and the brainstem by hypocretin/orexin deficiency explains why RBD may occur in narcolepsy. However, in narcolepsy, RBD is not very common and is usually not a bothersome symptom compared with

## KEY POINTS

- In patients with idiopathic rapid eye movement sleep behavior disorder, abnormal deposits of phosphorylated  $\alpha$ -synuclein are detected in peripheral organs outside the brain.
- Rapid eye movement sleep behavior disorder may be secondary to established neurodegenerative diseases (eg, Parkinson disease, spinocerebellar ataxias), autoimmune diseases (anti-IgLON5 disease, narcolepsy, paraneoplastic syndromes), focal brainstem lesions (ischemic infarct, tumors), and may be induced by medications (antidepressants).

**TABLE 5-2** Conditions Associated With Rapid Eye Movement Sleep Behavior Disorder**► Neurodegenerative Diseases**

Idiopathic Parkinson disease (25%–58% of the cases)  
 Parkinson disease with LRRK2 mutation (15%)  
 Parkinson disease with parkin2 mutation (a few descriptions)  
 Dementia with Lewy bodies (50%–70% of the cases)  
 Multiple system atrophy (90%–100% of the cases)  
 Mild cognitive impairment (a few descriptions)  
 Pure autonomic failure (a few descriptions)  
 Alzheimer disease (anecdotal cases)  
 Progressive supranuclear palsy (a few descriptions)  
 Guadeloupean parkinsonism (a few descriptions)  
 Frontotemporal dementia (anecdotal descriptions)  
 Corticobasal syndrome (anecdotal descriptions)  
 DJ1 mutations and parkinsonism-dementia-amyotrophic lateral sclerosis complex (anecdotal descriptions)  
 Amyotrophic lateral sclerosis (a few descriptions)  
 Neurodegeneration with brain accumulation type 1 (anecdotal descriptions)  
 Wilson disease (a few descriptions)  
 Huntington disease (a few descriptions)  
 Spinocerebellar ataxia type 3 (a few descriptions)  
 Spinocerebellar ataxia type 2 (a few descriptions)

**► Autoimmune Disorders**

Narcolepsy (30% of the cases)  
 Limbic encephalitis associated with antibodies to voltage-gated potassium channels/LIG1 (a few descriptions)  
 Anti-*N*-methyl-D-aspartate (NMDA) encephalitis (anecdotal descriptions)  
 Anti-Ma1 and anti-Ma2 encephalitis (anecdotal descriptions)  
 Anti-IgLON5 disease (100%)  
 Guillain-Barré syndrome (anecdotal descriptions)

**► Other Neurologic Conditions**

Myotonic dystrophy type 2 (anecdotal descriptions)  
 Autism (anecdotal descriptions)  
 Tourette syndrome (anecdotal descriptions)  
 Chiari malformations (anecdotal description)  
 Smith-Magenis syndrome (anecdotal description)  
 Möbius syndrome (anecdotal description)  
 Attention deficit hyperactivity disorder (anecdotal description)  
 Posttraumatic stress disorder (a few descriptions)

*Continued on page 1027*

**TABLE 5-2** Conditions Associated With Rapid Eye Movement Sleep Behavior Disorder *Continued from page 1026*

► **Structural Brain Lesions (Anecdotal Descriptions)**

Ischemic infarct  
Hemorrhage from cavernoma  
Tumors (astrocytoma, neurinoma, lymphoma)  
Demyelinating plaques in multiple sclerosis  
Limbic encephalitis  
Autosomal dominant leukodystrophy

► **Drugs That Can Cause or Worsen Rapid Eye Movement Sleep Behavior Disorder**

Antidepressants (especially selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs])  
Beta-blockers

**KEY POINTS**

- Antidepressants including tricyclics, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors can induce rapid eye movement sleep behavior disorder. Lipophilic beta-blockers such as bisoprolol may also trigger rapid eye movement sleep behavior disorder.
- Rapid eye movement sleep behavior disorder has been described in the new entity, anti-IgLON5 disease, characterized by the presence of autoantibodies against IgLON5 (a neuronal cell adhesion protein), and postmortem examination shows a tauopathy involving the brainstem and hypothalamus.

hypersomnia, cataplexy, and sleep fragmentation. RBD occurs in autoimmune disorders, paraneoplastic syndromes, tumors, strokes, and multiple sclerosis when the structures that regulate REM sleep atonia (medial magnocellular nucleus, subcoeruleus nucleus, amygdala) are damaged.

Antidepressants including tricyclics, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) can induce RBD. Lipophilic beta-blockers such as bisoprolol may also trigger RBD. Discontinuation of the offending drug is usually associated with the elimination of the clinical and video-polysomnographic features of RBD, suggesting that the parasomnia was simply a side effect of these drugs. However, in other cases, RBD persists, suggesting that the antidepressant may have unmasked an otherwise latent neurodegenerative process.

RBD has been described in the new entity, anti-IgLON5 disease.<sup>26,27</sup> This neurologic disorder is characterized by the presence of autoantibodies against IgLON5 (a neuronal cell adhesion protein) and the haplotypes DQB1\*0501 and DRB1\*1001, and postmortem ex-

amination shows a tauopathy involving the brainstem and hypothalamus. From a clinical point of view, there are a variety of neurologic (eg, gait instability, dysphagia, chorea, dementia, tiredness, hoarseness, dystonia, upward gaze palsy) and sleep (eg, insomnia, stridor, dream-enacting behaviors, hypersialorrhea during sleep, hypersomnia) abnormalities. Video-polysomnography shows a very complex sleep pattern characterized by sleep-breathing abnormalities (obstructive sleep apnea and inspiratory stridor secondary to vocal cord palsy) and by abnormal sleep architecture. Abnormal sleep architecture includes infrequent normal N1 and N2 sleep, normal N3 sleep with delta waves only in the second half of the night, periods of diffuse delta activity typical of normal N3 sleep mixed with spindles, poorly structured stage N2 sleep with spindles and K complexes, vocalizations and apparently intentional behaviors in non-REM sleep, and RBD of mild intensity characterized by very frequent limb and body jerks, but no vocalizations and no complex or finalistic (apparently goal-directed) behaviors. This entity affects people of both sexes older than

# KEY POINTS

- First-line drug treatment of rapid eye movement sleep behavior disorder symptoms are clonazepam or melatonin at bedtime.
- Patients with idiopathic rapid eye movement sleep behavior disorder are candidates for enrollment in neuroprotective trials.
- Nightmares are usually benign when isolated, but may be one of the features of several conditions such as rapid eye movement sleep behavior disorder, narcolepsy, sleep terrors, depression, posttraumatic stress disorder, and the effect of some medications.

the age of 50 and does not respond to immunotherapy.

**Management.** To minimize the risk of injury, protection measures are recommended to improve the safety of the sleep environment, such as sleeping in separate beds or bedrooms, removing dangerous objects from the bedroom, installing bed rails, or placing cushions on the floor next to the bed. First-line drug treatments of RBD symptoms are clonazepam and melatonin at bedtime, and either is effective in reducing dream-enacting intensity and frequency, but they do not impact, in idiopathic RBD cases, the risk for developing PD and DLB. The typical effective doses are clonazepam 0.25 mg to 2 mg and melatonin 3 mg to 12 mg at bedtime. Dopaminergic agents are not effective.<sup>55</sup>

It is debatable if physicians should inform the patient with idiopathic RBD that the parasomnia is associated with a risk for developing parkinsonism and dementia. The issue raises ethical and practical considerations. It is important to remark that (1) patients with idiopathic RBD feel well and have no motor or cognitive problems, (2) no interventions exist to stop the neurodegenerative process, and (3) the risk for conversion is not absolute and not imminent. For these reasons, some physicians argue against disclosing information that would lead to years of worry. If physicians are reluctant to disclose information, it is very likely that newly diagnosed patients with idiopathic RBD or their relatives will search on the Internet and find out the strong link between their parasomnia and a neurodegenerative disease. Patients may then think that their physician withheld important information regarding their health. The authors believe that early disclosure of the risk is an optimal approach to provide accu-

rate counseling. Physicians should inform patients with caution but with a determined attitude. The conversation should focus on the goals of good medical care, commitment, and encouraging periodic follow-up visits. Patients should learn that these routine visits will allow the earliest identification of parkinsonism and cognitive impairment and will enable appropriate management for enhancing quality of life. Also, patients should be informed that clinicians and researchers aim to design disease-modifying drug trials in the idiopathic RBD population, and patients with idiopathic RBD are candidates to be considered for enrollment in neuroprotective trials.

Of course, physicians do not need to give all this information at the initial visit, but can provide it on subsequent follow-up visits, depending on each individual patient.

# NIGHTMARES

Contrary to popular belief, dreams occur not only during REM sleep but also during all stages of non-REM sleep. Thus, nightmares (repeated occurrences of extended, dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity) may occur in all sleep stages. An important feature of nightmares is that, upon waking, the person remembers the unpleasant dream and is fully oriented and alert. Particularly in children, nightmares are isolated, transient, and benign. In these cases, education and reassurance that nightmares are harmless conditions are sufficient. See **Table 5-3** for the *ICSD-3* diagnostic criteria for nightmares.

Nightmares are usually benign when isolated but may be one of the features of several conditions such as RBD, narcolepsy, sleep terrors, depression, posttraumatic stress disorder, and the effect of some medications.



**TABLE 5-3** *International Classification of Sleep Disorders, Third Edition, Diagnostic Criteria for Nightmares<sup>a</sup>*

**Criteria A through C must be met for a diagnosis of nightmares**

- A. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity
- B. On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert
- C. The dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following:
  - 1. Mood disturbance (eg, persistence of nightmare affect, anxiety, dysphoria)
  - 2. Sleep resistance (eg, bedtime anxiety, fear of sleep/subsequent nightmares)
  - 3. Cognitive impairments (eg, intrusive nightmare imagery, impaired concentration, or memory)
  - 4. Negative impact on caregiver or family functioning (eg, nighttime disruption)
  - 5. Behavioral problems (eg, bedtime avoidance, fear of the dark)
  - 6. Daytime sleepiness
  - 7. Fatigue or low energy
  - 8. Impaired occupational or educational function
  - 9. Impaired interpersonal/social function

<sup>a</sup> Reprinted with permission from the American Academy of Sleep Medicine.<sup>4</sup>  
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Nightmares can be the side effect of medications (eg, beta-blockers, antidepressants, nicotine, or varenicline patches) or the effect of substance withdrawal (eg, alcohol). In RBD, dream content consists of situations where the patient is attacked or chased. The same content may occur in subjects with severe obstructive sleep apnea (Case 5-2) and periodic limb movement disorder, although they usually occur in N2 sleep. Nightmares in sleep terrors occur in N2 and N3 sleep and involve threats and the need to escape from something like a fire or a small room. Depression and obstructive sleep apnea are associated with nightmares consisting of frustration (eg, not finding the car in a

parking lot or not finishing tasks at work) or, in the case of sleep apnea, sometimes suffocation or drowning.

Therapy is warranted when recurrent nightmares cause significant stress and impairment in social, occupational, and other areas of functioning (eg, anxiety, fear of sleep, fatigue). For nightmares associated with posttraumatic stress disorder, prazosin 1 mg to 3 mg nightly has been shown to be beneficial, leading to its adoption for treatment of nightmares more broadly, although evidence for treatment of nightmares unassociated with posttraumatic stress is not established.<sup>55</sup> A mindfulness-based intervention known as dream image rehearsal therapy has also been reported to be successful in



# KEY POINTS

- Isolated sleep paralysis is a benign condition but can be a highly frightening situation when it first occurs. Secondary sleep paralysis is a feature of narcolepsy. Relevant neurologic and medical differential diagnoses must be ruled out.
- Sleep paralysis is termed hypnagogic when it occurs upon falling asleep and hypnopompic when it occurs upon awakening.

## Case 5-2

A 66-year-old man presented to a sleep center with a 3-year history of dream-enacting behaviors. He had been diagnosed with Parkinson disease 7 years earlier and was taking 2 carbidopa/levodopa 25 mg/100 mg tablets 3 times daily (total levodopa dosage of 600 mg/d) and the rotigotine patch (8 mg). Behaviors witnessed by his wife while the patient slept included gesturing, pointing out, smacking, kicking, talking, and shouting. He recalled having disturbing dreams such as fighting someone or having trouble finding his car keys. These abnormal behaviors and nightmares did not change after being treated with clonazepam (3 mg at bedtime) for 6 months. He was a habitual loud snorer and admitted to dozing off while watching television and reading magazines. He denied cognitive impairment. Neurologic examination was unremarkable.

Video-polysomnography showed an apnea-hypopnea index of 57 per hour, an arousal index of 65, minimal oxyhemoglobin saturation of 64%, and a decrease in slow-wave sleep percentage. Videotape analysis disclosed abnormal behaviors that appeared to be acting out a dream (ie, gesturing, kicking, talking) that only occurred during arousals at the end of most obstructive sleep apneic events. Behaviors displayed from arousals in rapid eye movement (REM) sleep were indistinguishable clinically from those occurring in non-REM sleep. REM sleep was characterized by muscle atonia. No increased tonic or phasic EMG activity occurred in the mentalis and four limb muscles. Epileptiform activity was not detected. The patient accepted treatment with continuous positive airway pressure (CPAP). A second polysomnographic study showed that CPAP titration eliminated snoring, apneic events, arousals, and oxyhemoglobin desaturations with an optimal pressure of 9 cm of H<sub>2</sub>O. A second video-polysomnography study also found normal REM sleep atonia. During follow-up visits, the patient reported good CPAP compliance, using the machine every night, with complete cessation of his abnormal sleep behaviors, unpleasant dreams, snoring, and daytime hypersomnolence.

**Comment.** Severe obstructive sleep apnea can mimic the characteristic symptoms of RBD. Video-polysomnography should be performed in subjects with suspected RBD to confirm or to exclude the presence of this parasomnia.

the management of nightmare disorder. Image rehearsal therapy involves “rewriting” the storyline, theme, or conclusions of a typical distressing nightmare to a more positive conclusion during wakefulness for 10 to 20 minutes daily, with hopes that this strategy improves the nightmarish dream content.<sup>55</sup>

## RECURRENT ISOLATED SLEEP PARALYSIS

Whereas in RBD, persisting muscle tone during REM sleep permits the occurrence of RBD behaviors, in recurrent isolated sleep paralysis, it is assumed that REM sleep muscle

atonia, otherwise a hallmark of physiologic REM sleep, persists and extends into wakefulness. Isolated sleep paralysis is a benign condition but can be experienced as a highly frightening situation when it first occurs. Secondary sleep paralysis is a feature of narcolepsy, and relevant neurologic and medical differential diagnoses (eg, hypokalemic periodic paralysis) must be ruled out.

Sleep paralysis is termed hypnagogic when it occurs upon falling asleep and hypnopompic when it occurs upon awakening. The characteristic clinical feature of sleep paralysis is

the complete inability to move (not only heaviness) in the presence of full wakefulness. Ancillary respiratory muscles are also affected from REM sleep atonia, and the diaphragm is the only respiratory muscle continuing to function during REM sleep. A sensation of difficulty breathing, sometimes associated with hallucinatory experiences, have contributed to the fact that sleep paralysis is recognized in different popular cultures.<sup>56</sup> Extrinsic eye muscles are unaffected. While no specific medical treatment beyond reassurance as to its ultimately physiologic and benign nature is recommended for recurrent isolated sleep paralysis, frequent triggers (eg, sleep deprivation, jet lag, comorbid obstructive sleep apnea triggering arousal) should be recognized and corrected or avoided. Differential diagnosis may include hypokalemic periodic paralysis, complex nocturnal visual hallucinosis, panic attacks, obstructive or central sleep apnea, and transient ischemic attack. However, the characteristic features of recurrent, short-lived, symmetrical paralysis with rapid recovery and a benign clinical course experienced only upon awakening from sleep are diagnostic historical features for recurrent isolated sleep paralysis. While sleep paralysis is listed among the REM-related parasomnias in the *ICSD-3*, it should be also noted that even in healthy persons, sleep paralysis may sometimes go along with hallucinatory experiences, namely, visual, acoustic, or tactile hallucinations of the perception of a person's presence. However, hypnagogic hallucinations are listed among the other parasomnias. In some cases, rudimentary low-volume vocalizations are also uttered during sleep paralysis.

## CONCLUSION

RBD is clinically characterized by dream-enacting behaviors and night-

mares. Video-polysomnography is needed to establish its diagnosis, showing abnormal behaviors and REM sleep without atonia. An optimal video-polysomnographic montage should include audio and EMG recording of the mental/submental and flexor digitorum superficialis muscles in the upper limbs. Correct diagnosis is important because other conditions may mimic RBD symptoms, and the idiopathic form may herald PD and DLB. Patients with idiopathic RBD are candidates for testing neuroprotective medications to halt the degenerative process and prevent the onset of parkinsonism and dementia. Recurrent sleep paralysis and nightmares are usually benign conditions, but, in some cases, are components of sleep disorders such as in narcolepsy, sleep terrors, and RBD.

## VIDEO LEGEND Supplemental Digital Content 5-1

**Rapid eye movement sleep behavior disorder.** A 63-year-old man with idiopathic rapid eye movement (REM) sleep behavior disorder showing typical prominent jerks during REM sleep.

[links.lww.com/CONT/A221](http://links.lww.com/CONT/A221)

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## KEY POINTS

- Ancillary respiratory muscles are also affected from rapid eye movement sleep atonia, and the diaphragm is the only respiratory muscle continuing to function during rapid eye movement sleep.
- The differential diagnosis for recurrent isolated sleep paralysis may include hypokalemic periodic paralysis, complex nocturnal visual hallucinosis, panic attacks, obstructive or central sleep apnea, and transient ischemic attack. However, the characteristic features of recurrent, short-lived, symmetrical paralysis with rapid recovery and a benign clinical course experienced only upon awakening from sleep are diagnostic historical features for recurrent isolated sleep paralysis.

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# Non-Rapid Eye Movement Sleep and Overlap Parasomnias

Muna Irfan, MD; Carlos H. Schenck, MD; Michael J. Howell, MD, FAAN

## ABSTRACT

**Purpose of Review:** This article reviews the spectrum of non-rapid eye movement (non-REM) sleep parasomnias, including sleepwalking, confusional arousals, and sleep terrors, which represent the range of phenotypic disorders of arousal from non-REM sleep that occurs in children and adults.

**Recent Findings:** The *International Classification of Sleep Disorders, Third Edition (ICSD-3)* classifies parasomnias according to the sleep stage they emerge from: REM, non-REM, or other. Demographics, clinical features, and diagnosis of non-REM parasomnias are reviewed in this article, and an up-to-date synopsis of guidelines for management strategies to assist in the treatment of these sleep disorders is provided.

**Summary:** The non-REM parasomnias are most common in children and adolescents but may persist into adulthood. They can be distinguishable from REM parasomnias and nocturnal epilepsies, and, importantly, may lead to injury. Additionally, other parasomnias in this spectrum include sleep-related eating disorder and sexsomnia. Overlap parasomnia disorder includes one or more manifestations of a non-REM parasomnia seen in combination with REM sleep behavior disorder, representing an apparent erosion of the normally distinct stages of non-REM and REM sleep. A similar yet much more extreme dissociation of states underlies *agrypnia excitata* and *status dissociatus*, which represent rare, severe dissociations between non-REM, REM, and wake states resulting clinically in oneiric behaviors and severe derangement of normal polysomnographic wake and sleep stage characteristics. Management of non-REM and overlap parasomnias and state dissociation disorders include ensuring bedroom safety and prescription of clonazepam or hypnosis, in select cases, although in children and adolescents with noninjurious behaviors, non-REM parasomnias are often age-limited developmental disorders, which may ultimately remit by adulthood, and, in these cases, counseling and education alone may suffice. Timely and accurate recognition of the non-REM and overlap parasomnias is crucial to limiting potential patient injury.

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Drs Irfan, Schenck, and Howell discuss the unlabeled/investigational use of benzodiazepines and melatonin for the treatment of parasomnias.

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## INTRODUCTION

Parasomnias are characterized by abnormal nocturnal behaviors, experiences, and autonomic responses emanating from sleep.<sup>1</sup> Parasomnias are categorized according to the sleep stage they emerge from as rapid eye movement (REM) sleep parasomnias, non-REM sleep parasomnias, or state-independent parasomnias (which are classified as

“other” in the *International Classification of Sleep Disorders, Third Edition [ICSD-3]*) (Table 6-1).<sup>1</sup> The key common clinical characteristics of non-REM parasomnias are recurrence of episodes of incomplete awakening from sleep and amnesia. These episodes can have variable clinical presentations of disruptive abnormal behavior, such as ambulation, eating, and talking during sleep. If



### KEY POINTS

- Parasomnias are categorized according to the sleep stage they emerge from as rapid eye movement sleep parasomnias, non-rapid eye movement sleep parasomnias, or other (state-independent) parasomnias.
- Non-rapid eye movement parasomnias occur mostly during slow-wave sleep (sleep stage N3) but can also arise from sleep stage N2.
- Any factor increasing the propensity for sleep fragmentation (eg, pain, restless legs syndrome symptoms and periodic limb movements, obstructive sleep apnea events, or extrinsic stimuli such as loud noises) can lead to partial cortical arousal with impaired consciousness.

**TABLE 6-1** Classification of Parasomnias<sup>a,b</sup>

- ▶ **Non-Rapid Eye Movement Sleep Parasomnias**
  - Confusional arousals
  - Sleepwalking (somnambulism)
  - Sleep terrors
  - Sleep-related eating disorder
  - Sexsomnia<sup>c</sup>
- ▶ **Other Parasomnias**
  - Exploding head syndrome
  - Sleep-related hallucinations
  - Sleep enuresis
  - Parasomnias due to a medical disorder
  - Parasomnias due to a medication or substance
  - Parasomnia, unspecified
- ▶ **Isolated Symptoms**
  - Sleeptalking (somniloquy)
- ▶ **Parasomnia Overlap Disorders<sup>c</sup>**
  - Status dissociatus<sup>c</sup>

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>

<sup>b</sup> Excludes rapid eye movement (REM)-related parasomnias.

<sup>c</sup> Not included in the *International Classification of Sleep Disorders, Third Edition*.

the patient's family. The general criteria for disorders of arousal from non-REM sleep are outlined in Table 6-2.<sup>1</sup>

### PATHOPHYSIOLOGY OF NON-RAPID EYE MOVEMENT SLEEP PARASOMNIAS

The varying clinical phenotypes of disorders of arousal from non-REM sleep include confusional arousals, sleepwalking, and sleep terrors; all these share the same presumed underlying pathophysiologic mechanism of an incomplete transition from non-REM sleep to the awake state when sleep-wake boundary dyscontrol occurs. Non-REM parasomnias occur mostly during slow-wave sleep (sleep stage N3) but can also arise from sleep stage N2.<sup>2</sup> Several physiologic phenomena can precipitate the occurrence of these parasomnias by impairing complete cortical arousal out of the sleep state. Any factor increasing the propensity for sleep fragmentation (eg, pain, restless legs syndrome [RLS] symptoms and periodic limb movements, obstructive sleep apnea [OSA] events, or extrinsic stimuli such as loud noises) can lead to partial cortical arousal with impaired consciousness.<sup>3</sup>

Disorders of arousal may be exacerbated by conditions that promote the homeostatic sleep drive, such as sleep deprivation and sedating medications,

left untreated, the nocturnal episodes can lead to clinical consequences in the patient, such as injuries and distress to

**TABLE 6-2** General Diagnostic Criteria for Disorders of Arousal<sup>a</sup>

- A. Recurrent episodes of incomplete awakening from sleep
- B. Lack of or inappropriate response to intervention or redirection during episodes
- C. Limited or no cognition or dream imagery
- D. Partial or complete amnesia for the event
- E. Nocturnal disturbance is not explained by other sleep, psychiatric, or medical disorder or medication/substance use

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>

by increasing the threshold for arousal. These conditions hinder the normal sleep-wake transition by enhancing sleep inertia and thus lead to emergence of the abnormal nocturnal behavior.

Pressman<sup>4</sup> has eloquently conceptualized a model for the non-REM disorders of arousal. A patient with an intrinsic *predisposition* is *primed* by influences such as sedating medications that hinder normal cortical arousal. Consequently, *precipitating* factors such as OSA or environmental disruption (eg, noise) trigger a disordered arousal from non-REM sleep (this is analogous to, yet distinct from, the 3P model for the etiology of insomnia disorder discussed in the article “Chronic Insomnia Disorder” by Alon Y. Avidan, MD, MPH, FAAN, and David N. Neubauer, MD,<sup>5</sup> in this issue of *Continuum*).

Non-REM parasomnia behaviors are manifested as arousal associated with disorientation, amnestic behavior, and confusion. The individual becomes ensnared in a state between non-REM and wakefulness due to disintegration of discrete boundaries between sleep and wake states. The physiologic responses are reminiscent of primordial instinctive behavioral manifestations, such as locomotion, aggression, and feeding, in conjunction with amnestic behavior during these nocturnal episodes.<sup>1</sup> The higher prevalence of non-REM parasomnias in the pediatric population also suggests that developmental immaturity of sleep-wake boundary regulation is an additional vulnerability factor that occurs at younger ages.<sup>1</sup>

In addition to the environmental and metabolic factors discussed, genetic elements have been suggested. Studies have demonstrated a high prevalence of human leukocyte antigen (HLA) DQB1\*05:01 and HLA DQB1\*04 alleles in various non-REM parasomnias.<sup>6,7</sup> An autosomal dominant trait for sleep-

walking at chromosome 20 has also been identified.<sup>8</sup> Factors and conditions associated with the arousal parasomnias are listed in Table 6-3.

## CONFUSIONAL AROUSALS

Confusional arousals are partial awakenings from slow-wave sleep, also known as sleep drunkenness and Elpenor syndrome. The individual typically sits up in a disoriented state and has some automatic behavior, such as mumbling, low-intensity vocalizations, confused motoric activity without

## KEY POINT

■ Conditions that exacerbate disorders of arousal include those that promote the homeostatic sleep drive, such as sleep deprivation and sedating medications, by increasing the threshold for arousal.

**TABLE 6-3 Factors and Conditions Associated With Arousal Parasomnias**

### ► Predisposing Factors

#### Genetic factors

Human leukocyte antigen (HLA) DQB1\*05 and HLA DQB1\*04 alleles

Chromosome 20q12-q13.12 locus

#### Maturation factors

#### Ambulating disorders

Restless legs syndrome (for sleepwalking)

### ► Priming/Precipitating Factors

#### Enhancing slow-wave sleep

Sleep deprivation

Circadian misalignment

#### Impairing cortical arousal

Central nervous system suppressant drugs

#### Increasing sleep fragmentation

Extrinsic stimuli

Periodic limb movements

Obstructive sleep apnea

Medical disorders such as gastroesophageal reflux disease

Psychiatric disorders and stress

**KEY POINTS**

- Confusional arousals are partial awakenings from slow-wave sleep. The individual typically sits up in a disoriented state and has some automatic behavior, such as mumbling, low-intensity vocalizations, confused motoric activity without ambulation, and sympathetic hyperactivity.
- Sleepwalking is the disorder of arousal manifesting with prominent ambulatory behavior.

ambulation, and sympathetic hyperactivity. Confusional arousals are more common in pediatric populations, the prevalence being up to 17%,<sup>9</sup> while in adults, the prevalence is reported to be only 3% to 4%.<sup>10</sup> The episode is typically brief in duration, lasting for a few minutes, and associated with diminished or altered responsiveness to external stimuli. Occasionally, the event might be prolonged, particularly with sedative hypnotic use.<sup>11,12</sup> Partial or complete amnesia is noted, with an absence or only vague recollection of the episode afterward. According to *ICSD-3*, several criteria should be met for the diagnosis, as outlined in Table 6-4.<sup>1</sup>

**TABLE 6-4 Diagnostic Criteria for Confusional Arousal<sup>a</sup>**

- A. The disorder fulfills general criteria for non-rapid eye movement sleep disorders of arousal
- B. The episodes consist of patient demonstrating confused behavior after arousal while in bed
- C. Absence of terror or ambulation out of bed

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>

**SLEEPWALKING**

Sleepwalking (somnambulism) is the disorder of arousal manifesting with prominent ambulatory behavior.<sup>1</sup> A large 2015 prospective study revealed the overall pediatric prevalence (ages 2.5 to 13 years) of sleepwalking to be 29.1%, with the peak observed at age 10.<sup>13</sup> The prevalence increased to 47.4% for children with one parent with a history of sleepwalking and up to 61.5% for children with both parents

having a history of sleepwalking, supportive of a significant hereditary influence.<sup>13</sup> The prevalence of sleepwalking is decreased in adults, seen in only 1% to 4%,<sup>1,13</sup> although a 2014 study proposed that noninjurious sleepwalking is actually 12%, much higher than previously recognized.<sup>14</sup>

The nocturnal episodes can range from aimless wandering to complex, protracted, inappropriate behaviors, such as urinating in the closet, driving an automobile, or leaving the house unclothed in extreme weather conditions.<sup>1</sup> During an episode, sleepwalkers typically do not respond to attempts at redirection. Forceful restraining is not advised unless a high risk for injury exists. Occasionally, unintentional self-injurious actions, such as walking off a balcony or operating a motor vehicle, can result in grave consequences.<sup>15</sup> Sleepwalking tends to occur in the first half of the night, akin to the other non-REM disorders of arousal, and is related to the greater predominance of slow-wave sleep (sleep stage N3) in the first few hours of sleep. The *ICSD-3* diagnostic criteria for sleepwalking are listed in Table 6-5.

In adults, sleepwalking is frequently associated with other sleep disorders, such as RLS and OSA, as well as with use of sedative hypnotic medications,

**TABLE 6-5 Diagnostic Criteria for Sleepwalking<sup>a</sup>**

- A. The disorder fulfills general criteria for non-rapid eye movement sleep disorders of arousal
- B. Arousals are associated with ambulation and other complex behaviors out of bed

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>

in particular, the commonly prescribed benzodiazepine receptor agonists. Other than the priming and precipitating conditions previously mentioned, other medical conditions such as vitiligo, hyperthyroidism, migraines, febrile illness, head injury, encephalitis, stroke, and chronic pain syndrome have also been implicated.<sup>1,16</sup> In addition to the benzodiazepine receptor agonists,<sup>11</sup> a wide variety of other medication types have been implicated as provoking influences for sleepwalking, including antidepressants (amitriptyline, bupropion, paroxetine, mirtazapine), antipsychotics (quetiapine, olanzapine), antihypertensives (propranolol, metoprolol), antiepileptic drugs (topiramate), antiasthma agents (montelukast), and antibiotics (fluoroquinolones).<sup>1,12</sup>

A common and clinically relevant scenario is zolpidem-induced sleepwalking, among other amnestic behaviors during sleep, such as sleep-related eating disorder, often associated with the predisposing factor of underlying RLS. Since RLS frequently mimics insomnia,<sup>1</sup> the use of hypnotic drugs in patients with RLS is unfortunately common and may lead to sleepwalking and other related amnestic behaviors during sleep.<sup>12</sup> Thus, caution may be indicated when a sedative hypnotic is given to patients predisposed to ambulation due to RLS and motor restlessness or with underlying cognitive impairments, especially those with memory and executive dysfunction that may disinhibit amnestic behaviors and the primitive instinct of locomotion; in these settings, sleepwalking and other amnestic behaviors may emerge as complications of hypnotic therapy.<sup>11,12</sup>

## SLEEP TERRORS

Sleep terrors (also known as night terrors or *pavor nocturnus*) are a dramatic disorder of arousal that start with a

piercing scream at the onset of an abrupt arousal with autonomic hyperactivity and behavioral manifestation of intense fear. The prevalence of sleep terrors in children varies widely, from 14.7% to 56%.<sup>1,13</sup> In adults, the prevalence is reported as much lower at 2.2%,<sup>1,11</sup> with a relatively constant rate of 2.3% to 2.6% in those 15 to 64 years of age, decreasing to 1% in those older than 65 years of age.<sup>1</sup>

Sleep terrors consist of episodes of intense fright accompanied by loud crying or screaming in which the patient appears terrified and inconsolable. Increased autonomic activity results in tachypnea, tachycardia, mydriasis, diaphoresis, and increased muscle tone.<sup>1</sup> Patients are generally amnestic for episodes of sleep terror, although occasionally in adults, partial amnesia might be noted with vague recollection of a fragment of apparent dream mentation associated with the experience, such as a description of the ceiling collapsing or a fire in the bedroom.<sup>12</sup> Typically, the behaviors are noninjurious but can cause significant parental distress and sleep disruption (Case 6-1). Attempts to console the patient can lead to paradoxical increase in aggression.<sup>12</sup> The diagnostic criteria for diagnosis of sleep terrors are listed in Table 6-6.<sup>1</sup>

## CLINICAL EVALUATION OF NON-RAPID EYE MOVEMENT DISORDERS OF AROUSAL

Comprehensive historical accounts of witnessed events obtained from the patient and a collateral historian, especially the parents in children or a bed partner in adults, is crucial for the diagnosis of parasomnia disorders. The patient's signs during an event further aid in supporting the suspected diagnosis (eg, in a patient with night terrors, the patient may exhibit tachycardia, palpitations, and diaphoresis,

### KEY POINTS

- Sleep terrors consist of episodes of intense fright accompanied by loud crying or screaming in which the patient appears terrified and inconsolable. Increased autonomic activity results in tachypnea, tachycardia, mydriasis, diaphoresis, and increased muscle tone.
- Comprehensive historical accounts of witnessed events obtained from the patient and a collateral historian, especially the parents in children or a bed partner in adults, is crucial for diagnosis of parasomnia disorders.

**Case 6-1**

A 5-year-old girl presented with her parents, who described distressing nightly behaviors that had been occurring over the past year. After going to sleep at about 8:00 PM, she would awaken with a scream at about 11:00 PM seemingly confused and very difficult to console. Attempts to calm her only resulted in increased agitation. During an episode, the child would sweat profusely and breathe rapidly, and her heart raced. Her mother felt that during these episodes the girl was “possessed by a demon.” She recently contacted emergency services as she was convinced the child was having a seizure. These events lasted approximately 15 minutes, and then the girl fell back asleep. In the morning, she had no recollection of events. The child’s napping schedule had recently changed as she had started kindergarten, resulting in much shorter naps. She had a normal medical history. Her examination was normal.

The patient was diagnosed with sleep terrors, and her parents were reassured that this condition did not represent a neurologic emergency. Efforts were made with the child’s school to allow for a longer nap, which led to resolution of the episodes. At 1-year follow-up, the sleep terrors had not recurred.

**Comment.** This case demonstrates several clinical aspects typical of sleep terrors, including age-related onset during childhood, high parental concern, nighttime sleep disturbance, and association with a stressor such as change in school setting and daytime napping behaviors. In this case, liberalizing the patient’s daytime napping led to decreased sleep homeostatic drive at night and led to resolution of the child’s sleep terror events.

which help to distinguish the diagnosis from other disorders of arousal such as sleepwalking). In cases in which details are not clear, video-EEG poly-

somnography can be performed to assist in the diagnosis.

**DIFFERENTIAL DIAGNOSIS OF NON-RAPID EYE MOVEMENT PARASOMNIAS**

The non-REM disorders of arousal should be distinguished from other sleep-related disorders with potential similar clinical presentation, which include REM sleep behavior disorder (RBD), sleep-related epilepsy, sleep-related dissociative disorder, alcohol- and drug-related behavioral manifestations during sleep, OSA, and psychogenic spells or malingering.

RBD may be differentiated from non-REM disorders of arousal by several distinctive features, including complex dream enactment behaviors, which parallel described dream mentation and often involve defense against attack or aggression, and its more frequent occurrence in the second half of the night. Video-polysomnography can help

**TABLE 6-6** Diagnostic Criteria for Sleep Terrors<sup>a</sup>

- A. The disorder fulfills general criteria for non-rapid eye movement sleep disorders of arousal
- B. The arousal is characterized by sudden fright manifested by terrifying scream/vocalization at the onset
- C. Events comprising intense fear and signs of autonomic arousal, mydriasis, tachycardia, tachypnea, and diaphoresis

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>



differentiate these disorders, sometimes directly by capturing actual events but also by assessing for the loss of skeletal muscle atonia (as measured by EMG) during REM sleep, which is supportive of the alternative diagnosis of RBD. For more information on RBD, refer to the article “Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias” by Birgit Högl, MD, and Alex Iranzo, MD,<sup>17</sup> in this issue of *Continuum*. Sleep-related epilepsy is exhibited by stereotypical repetitive behavior with bicycling, rocking, or running leg movements or, less often, by episodic nocturnal wandering episodes. In such cases, a full EEG montage should be conducted simultaneously with polysomnography to delineate the nature of these events. A history of significant psychosocial pathology, including sexual abuse, should raise concern for a possible diagnosis of a dissociative disorder. Aggravating factors, such as RLS and OSA, should also be carefully screened for and addressed, since effective treatment of these sleep comorbidities may reduce the propensity that provoke arousals from non-REM sleep, thereby decreasing the occurrence of non-REM disorders of arousal. Clinical characteristics of various parasomnias are listed in Table 6-7, and their polysomnographic findings are listed in Table 6-8.

## POLYSOMNOGRAPHIC EVALUATION OF PARASOMNIAS

The American Academy of Sleep Medicine (AASM) has published practice guidelines for the evaluation of parasomnias.<sup>18</sup> According to the AASM, comprehensive in-laboratory video-polysomnography is indicated if the parasomnias are:

- Atypical or unusual in terms of age, onset, duration, or specific behavior
- Frequent in occurrence, (more than 2 or 3 times a week)

- Potentially injurious
- Potentially originating from epileptogenic activity, if prior evaluation has been inconclusive

These practice parameters further recommend use of expanded EEG and EMG channels with good-quality video.<sup>18</sup>

For pediatric cases, the AASM suggests performing comprehensive video-polysomnography, with extended EEG and EMG montages if OSA is suspected or parasomnia-related arousals are violent.<sup>19</sup> The purpose of such an evaluation is to identify a reversible sleep disorder for which treatment could lead to resolution of the parasomnia and prevention of injury. Because of their intermittent nature, nocturnal episodes might not be recorded during a single-night study, but features such as non-REM sleep instability, epileptiform abnormalities, and changes in REM sleep atonia can help support a clinical diagnosis. The yield can be increased significantly by the combination of prior sleep deprivation with forced awakening from auditory stimuli, but this approach is only rarely applied in clinical practice and should be pursued only with appropriate oversight, such as driving restriction before and after the study and seizure/injury precautions in the sleep laboratory.<sup>19</sup>

In confusional arousals, sleep terrors, and sleepwalking, a buildup of hypersynchronous delta frequency EEG activity is variably associated with the arousal from sleep or may occur preceding the event. Following arousal, persistent slow cortical activity is variable, evolving into either normal waking background alpha activity or a return to the non-REM sleep state.<sup>12</sup> A segment of a typical polysomnographic tracing of confusional arousal is illustrated in Figure 6-1.

## KEY POINT

- For pediatric parasomnias, the American Academy of Sleep Medicine suggests performing comprehensive video-polysomnography, with extended EEG and EMG montages if obstructive sleep apnea is suspected or parasomnia-related arousals are violent.

**TABLE 6-7** Distinguishing Clinical Characteristics of Various Parasomnias

Parasomnia	Behavior	Autonomic Symptoms	Amnesia	Provoking Factors	Sex	Timing	Duration
Confusional arousal	Disoriented, simple to complex movements in the bed	Absent	Present	Sleep deprivation with forced awakening	No predominance, but injurious in males	First part of night	Several minutes, rarely prolonged
Sleepwalking	Ambulation, leaving the bed, wandering	Absent	Present	Sleep deprivation with forced awakening, restless legs syndrome	No predominance, but injurious in males	First part of night	Several minutes to prolonged
Sleep terrors	Distraught, agitated, screaming, inconsolable	Present	Present	Sleep deprivation with forced awakening	No predominance, but injurious in males	First part of night	Several minutes
Sleep-related eating disorder	High-calorie, bizarre eating after arousal from sleep	Absent	Present/variable recall	Sleep deprivation, restless legs syndrome, hypnotic use	Females more than males	Usually first part of night	Several minutes
Sleep enuresis	Loss of bladder control while asleep	Absent	Present	Sleep deprivation, increased fluid intake	Males more than females	Anytime	Seconds to minutes
Sexsomnia	Abnormal sexual behavior during sleep/partial arousal	Absent	Present	Sleep deprivation	Males more than females	Anytime	Minutes
Rapid eye movement (REM) sleep behavior disorder	Dream-enacting movements/vocalizations	Absent	Variable recall	None	Males more than females	About 2 hours after sleep onset	Seconds to minutes

**KEY POINT**

- The primary goal of managing parasomnias is to ensure the safety of the patient and cosleeper.

**MANAGEMENT OF NON-RAPID EYE MOVEMENT PARASOMNIAS**

Various strategies to control non-REM parasomnias are discussed below.

**Environmental Safety**

The primary goal of managing parasomnias is to ensure the safety of the patient and cosleeper. Environmental

modifications (eg, removing sharp or otherwise potentially harmful objects, furniture, and weapons from the bedroom; securing windows and other outlets; using door alarms) may prevent problematic consequences. Careful consideration should be given to addressing any reversible predisposing, priming, or precipitating factors, as discussed in the

**TABLE 6-8** Differentiating Polysomnographic Findings of Various Parasomnias

Parasomnia	Sleep Stage	Non-Rapid Eye Movement (REM) Instability	REM Sleep Atonia	Other Features
Confusional arousal	Non-REM	Present	Present	Hypersynchronous EEG delta activity
Sleepwalking	Non-REM	Present	Present	Restless legs syndrome
Sleep terrors	Non-REM	Present	Present	Increased heart rate
Sleep-related eating disorder	Non-REM	Present	Present	Restless legs syndrome, periodic limb movements, rhythmic masticatory muscle activity
Sleep enuresis	Non-REM/REM	Present	Present	
Sexsomnia	Non-REM	Present	Present	
REM sleep behavior disorder	REM	Absent	Absent	Periodic limb movements, irregular heart and respiratory rate

EEG = electroencephalogram.

section on pathophysiology. In particular, treatment of any comorbid sleep disorders, such as OSA and RLS, and removal of offending sedative agents significantly reduce the occurrence of disorders of arousal.<sup>20</sup>

### Pharmacotherapy

If the parasomnia behavior persists after treatment of comorbid sleep conditions and removal of offending drugs and precipitating factors, then pharmacologic intervention can be considered. The evidence basis for pharmacotherapy of the parasomnias is extremely sparse and, at times, contradictory. Benzodiazepines and antidepressants are the mainstay of pharmacotherapy, depending on the type of disorder of arousal. Clonazepam is frequently used as a first-line agent to treat non-REM parasomnias of disordered arousal, although other intermediate and long-acting benzodiazepines may also be used. In a series of 69 patients with sleepwalking and sleep terrors treated with clonazepam and other benzodiaz-

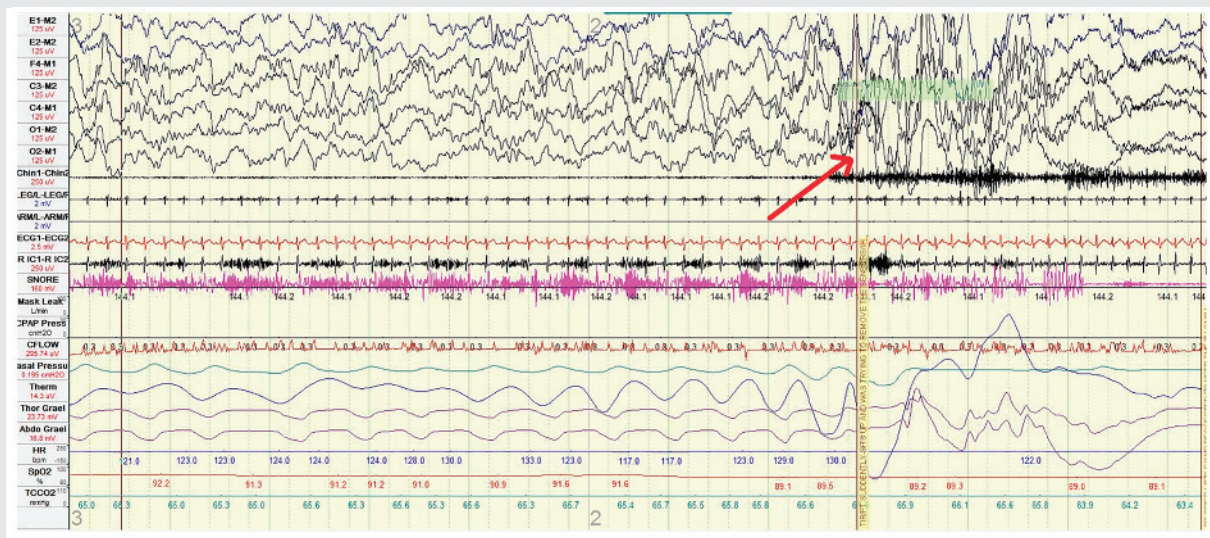
epines, 86% of patients showed significant improvement after an average follow-up of 3.5 years with sustained benefit.<sup>21</sup> Various serotonergic antidepressants have also been used for the treatment of non-REM parasomnias, especially for sleep terrors. One report showed a substantial response to imipramine in two patients with sleepwalking and sleep terrors,<sup>22</sup> while other case reports suggested convincing responses to trazodone<sup>23</sup> or paroxetine.<sup>24</sup> Antidepressants may improve sleep terrors by virtue of serotonergic effects on the mesencephalic periaqueductal gray matter.<sup>24</sup>

Behavioral strategies, such as psychotherapy, have also been employed for treatment of non-REM parasomnias with some success.<sup>25</sup> For benign parasomnias such as confusional arousals and sleep terrors in children, parents can be reassured about the generally noninjurious nature of the episodes and informed that events are frequently outgrown.

For persistent episodes of sleep terror in children, anticipatory awakenings

### KEY POINTS

- Treatment of any comorbid sleep disorders, such as obstructive sleep apnea and restless legs syndrome, and removal of offending sedative agents significantly reduce the occurrence of disorders of arousal.
- Clonazepam is frequently used as a first-line agent to treat non-rapid eye movement parasomnias of disordered arousal, although other intermediate and long-acting benzodiazepines may also be used.



**FIGURE 6-1** A 30-second polysomnographic tracing showing an arousal arising from sleep stage N3 (slow-wave sleep) (red arrow), showing hypersynchronous slow-wave activity and increase in muscle tone followed by normal wakefulness.

#### KEY POINTS

- For persistent episodes of sleep terrors in children, anticipatory awakenings 15 to 20 minutes before the typical time of occurrence has been shown to be highly effective in aborting the episodes.
- Sleep-related eating disorder is a condition characterized by recurrent episodes of typically amnesic binge eating of high-calorie food and sometimes bizarre pica-type ingestions after partial arousal from non-rapid eye movement sleep.

15 to 20 minutes before the typical time of occurrence has been shown to be highly effective in aborting the episodes.<sup>25</sup> Hypnotherapy has also been employed, with variable benefit from 27% to 87% reported in different case series for non-REM parasomnias.<sup>26</sup>

#### SLEEP-RELATED EATING DISORDER

Sleep-related eating disorder is a condition characterized by recurrent episodes of typically amnesic binge eating of high-calorie food and sometimes bizarre pica-type ingestions after partial arousal from non-REM sleep. The community prevalence of sleep-related eating disorder is currently not well characterized. Schenck and colleagues<sup>27</sup> found the prevalence of sleep-related eating disorder was 0.5% in a sleep clinic referral population. In college students, the occurrence was 4.6%,<sup>28</sup> and sleep-related eating disorder was found to affect 3.4% of patients in a depression clinic.<sup>29,30</sup> Sleep-related eating disorder has a 60% to 83% female preponderance, consistent with

eating disorders and incongruent with other disorders of arousal.<sup>1,30</sup>

The episodes of sleep-related eating in sleep-related eating disorder are not driven by hunger but seem to comprise involuntary compulsive eating after partial arousal from sleep. Episodes consist of ingestion of peculiar combinations of items; carbohydrate-rich foods; or inedible or toxic materials such as raw or frozen meat, pet food, or buttered cigarettes. Sleep-related eating disorder can lead to multiple adverse consequences, such as weight gain, injuries sustained from careless handling of food items during an episode, precipitation or exacerbation of diabetes mellitus, hypercholesterolemia, or dental caries. The frequency of episodes ranges from a few times a week to multiple times per night.<sup>1</sup> The criteria for diagnosis of sleep-related eating disorder are listed in **Table 6-9**.<sup>1</sup>

The pathophysiologic mechanism of sleep-related eating disorder is not established, although it has been proposed that several heterogeneous factors may play a causative role. Most



researchers agree that sleep-related eating disorder is a variant of sleepwalking since it is characterized by partial or incomplete arousals from sleep, involves ambulation culminating in feeding behavior, and is affected by the usual predisposing influences for non-REM disorders of arousal, especially RLS, as well as other precipitating conditions as previously discussed.<sup>28</sup> Patients with sleep-related eating disorder share many similarities with somnambulists, including that both conditions originate from non-REM sleep and that 60% of patients with sleep-related eating disorder have a history of past or concurrent sleepwalking (Case 6-2).<sup>1,27,30</sup> Wakeful nocturnal eating is a common nonmotor manifestation of RLS; thus, misclassification of RLS as insomnia and resulting treatment with sedative hypnotic medication, especially zolpidem, can lead to the emergence of amnesic sleep-related eating disorder.<sup>11,12,31</sup>

Zolpidem is the most common agent that induces sleep-related eating disorder, but a wide range of other psychotropic medications, including benzodiazepines, mirtazapine, quetiapine, lithium carbonate, and anticholinergic drugs, have also been reported.<sup>1</sup> Several other factors have been associated with sleep-related eating disorder, including alcohol and other substance use, cessation of smoking, acute stress, onset of narcolepsy, autoimmune hepatitis, and encephalitis.<sup>1</sup>

Sleep-related eating disorders should be distinguished from other conditions such as night eating syndrome and the nocturnal occurrence of other eating disorders, such as bulimia nervosa, binge eating disorder, binge/purge type anorexia nervosa, and Kleine-Levin syndrome. Night eating syndrome is characterized by excessive eating at night before bedtime or after awakening from sleep but, unlike sleep-related eating disorder, is associated with fully preserved awareness and intentional eating. In contrast to daytime eating disorders, compensatory behavior such as induced vomiting or laxative use is not noticed in sleep-related eating disorder, although other eating disorders can occur concurrently. Kleine-Levin syndrome is a complex disorder of recurrent periodic hypersomnia, cognitive impairment, hypersexuality, and hyperphagia during wakefulness

linergic drugs, have also been reported.<sup>1</sup> Several other factors have been associated with sleep-related eating disorder, including alcohol and other substance use, cessation of smoking, acute stress, onset of narcolepsy, autoimmune hepatitis, and encephalitis.<sup>1</sup>

## KEY POINTS

- Most researchers agree that sleep-related eating disorder is a variant of sleepwalking since it is characterized by partial or incomplete arousals from sleep, involves ambulation culminating in feeding behavior, and is affected by the usual predisposing influences for non-rapid eye movement disorders of arousal.
- Night eating syndrome is characterized by excessive eating at night before bedtime or after awakening from sleep but, unlike sleep-related eating disorder, is associated with fully preserved awareness and intentional eating.

**TABLE 6-9 Diagnostic Criteria for Sleep-Related Eating Disorder<sup>a</sup>**

- A. Recurrent episodes of dysfunctional eating occurring after arousal from main sleep period
- B. Presence of at least one of the following with recurrent involuntary eating
  - 1. Consumption of peculiar form or combination of food or inedible/toxic substances
  - 2. Sleep-related injurious/potentially injurious behavior noted during food preparation/pursuit
  - 3. Adverse consequences from recurrent nocturnal eating
- C. Partial or complete loss of awareness during the episode with subsequent impaired recall
- D. Disturbance is not explained by another sleep, mental, or medical disorder or medication/substance use

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>



**KEY POINT**

■ Dopamine agonists and topiramate have been used as pharmacotherapy for sleep-related eating disorder.

**Case 6-2**

A 44-year-old woman presented with amnesic nocturnal eating, which had resulted in a 20 kg (44 lb) weight gain over the previous 6 months. She experienced events involving sleepwalking to the kitchen and eating large portions of chocolate, peanut butter, and crackers. She would often wake up with a distended abdomen and chocolate spread on her fingers. She was found once by her husband, who said that she was “in a trance.” These events occurred approximately 4 to 5 times per week. Her diabetes mellitus was poorly controlled, and her dentist found three new dental caries.

These behaviors began after she started receiving zolpidem for “insomnia.” She had been reluctant to stop the drug since it was helping her fall asleep at night. However, further careful history revealed that she did not have hypervigilant insomnia, but instead her difficulty falling asleep was related to overwhelming discomfort in her legs compelling her to move her legs and walk at night. Before zolpidem therapy, she would often spend hours awake at night ambulating through the house and sometimes having a small snack.

The patient was diagnosed with sleep-related eating disorder and restless legs syndrome (RLS). Zolpidem was discontinued and pramipexole started, which resolved the difficulty with sleep initiation, and she had no further episodes of sleep-related eating disorder.

**Comment.** This case is a classic example of insomnia caused by RLS mistreated with zolpidem. She had no recollection of the nocturnal eating episodes with preference for carbohydrate-rich food items, which led to consequences such as poor oral hygiene and hyperglycemia. Thus, it is important to recognize this condition and address it in a timely manner. The treatment of underlying RLS not only improved her insomnia but also controlled the sleep-related eating disorder episodes.

with eventual return to baseline and thus can be easily separated from the symptomatology of sleep-related eating disorder. For more information on Kleine-Levin syndrome, refer to the article “Narcolepsy and Other Central Hypersomnias” by Yves Dauvilliers, MD, PhD, and Lucie Barateau, MD,<sup>32</sup> in this issue of *Continuum*.

The goal of treatment in sleep-related eating disorder is to eliminate any precipitating factors, such as hypnotic medications, and to recognize and treat any contributing comorbid sleep disorders, especially RLS. Removal of any offending drug, along with treatment of RLS and OSA, has been shown to resolve many cases of sleep-related eating disorder.<sup>29–31</sup> Dopamine agonists and topiramate have been used as

pharmacotherapy for sleep-related eating disorder. In an original case series, Schenck and colleagues<sup>33</sup> showed improvement in 52% of patients (14 of 27) who received dopamine agonist agents. A randomized controlled trial of pramipexole up to 0.36 mg/d showed decrease in nocturnal activity by actigraphy and subjective improvement in sleep.<sup>34</sup> Topiramate has been proposed to exert anorexigenic actions.<sup>29</sup> According to Winkelman,<sup>35</sup> 68% of patients responded to topiramate, with a mean dose of 135 mg/d, but the discontinuation rate was high because of side effects. Schenck and Mahowald<sup>36</sup> also showed good response with topiramate treatment, which was well tolerated over 1.8 years.

## SEXSOMNIA

Neurologists should be aware of sexsomnia for several reasons. Neurologists are often consulted for evaluation of unusual behaviors, including sleep-related abnormal sexual behaviors (sexsomnia). Rarely, sexual behavior may arise from nocturnal seizures, which can often be successfully treated, and sexsomnia may be comorbid with neurologic disorders such as Parkinson disease and narcolepsy.

The first classification of sleep-related disorders associated with abnormal sexual behaviors and experiences was published in 2007,<sup>37</sup> with an update in 2015.<sup>38</sup> Sexsomnia and sleep-related eating disorder are considered “appetitive” parasomnias, and they can be comorbid in the same patient. Sexsomnia is classified as a subtype of non-REM parasomnia disorders of arousal in *ICSD-3*,<sup>1</sup> with sexual behaviors that emerge during partial arousals from slow-wave (delta or stage N3) sleep, as is typical of the other non-REM parasomnias.

In a large series of 49 patients, sexsomnia was male predominant (75%), with a mean age of onset of 28 years and mean age at presentation of 35 years. A broad range of sexual behaviors was reported, including sexual intercourse/attempted intercourse (49%), fondling the bed partner (40%), agitated/assaultive sexual behaviors (37%), masturbation (23%), sexsomnia with minors (20%), sexual vocalizations (19%), and spontaneous sleep orgasm (4%). Not surprisingly, sexsomnia can lead to adverse legal consequences. The forensic implications of sexsomnia have recently been reviewed.<sup>38</sup> Shift work was a trigger for sexsomnia in one predisposed patient, and selective serotonin reuptake inhibitor (SSRI) therapy for depression was a trigger for sexsomnia in another patient. In four cases of sexsomnia

associated with Parkinson disease, onset was noted with the initiation or dose increase of pramipexole therapy. None of the patients had a prior history of parasomnia, sexual disorder, or impulse control disorder. A detailed medication history with the bed partner’s assistance is critical in the evaluation of a patient with sexsomnia, along with a detailed history of any parasomnia, sleep-disordered breathing, medical-neurologic-psychiatric problems, or family history.

Treatment data are limited; however, in one series, 86% of patients had control of sexsomnia with bedtime clonazepam, and 100% (4 of 4) of patients with comorbid OSA had resolution with control of OSA on nasal continuous positive airway pressure.

Ten cases of ictal/presumed ictal sexsomnia have been described, demonstrating a striking contrast between the high rate of recall for ictal sexsomnia episodes and the virtually complete amnesia for sexsomnia (parasomnia) episodes in all but two cases. In the 5 of 7 patients with reported treatment data, antiepileptic drug therapy completely suppressed the ictal sleep-related sexual seizures.<sup>38</sup>

## PARASOMNIA OVERLAP DISORDER

Parasomnia overlap disorder is a condition with clinical features of both non-REM parasomnias and RBD. While overlap parasomnia disorder is currently classified as a subtype of REM parasomnias,<sup>1</sup> some believe it may be a distinct entity because of several differentiating features, such as occurrence at a younger age and more frequent presentation with non-REM parasomnias compared to REM-related behaviors.<sup>39,40</sup> Overlap parasomnia disorder can also be seen secondary to various disorders such as narcolepsy, multiple sclerosis, brain tumors,

### KEY POINTS

- Sexsomnia is classified as a subtype of non-rapid eye movement parasomnia disorders of arousal in the *International Classification of Sleep Disorders, Third Edition*.
- Parasomnia overlap disorder is a condition with clinical features of both non-rapid eye movement sleep parasomnias and rapid eye movement sleep behavior disorder.

**KEY POINTS**

- Status dissociatus is a state of complete disintegration of wake/non-rapid eye movement/rapid eye movement sleep boundaries that is without identifiable sleep stages and with behavioral and motor manifestations of oneirism (dream-enactment behaviors).
- Agrypnia excitata is an extreme form of status dissociatus, with near-continuous motor and sympathetic hyperactivity, loss of N3 sleep stage (slow-wave) architecture, and dissociation of conventional non-rapid eye movement sleep markers.

rhombencephalitis, brain trauma, spinocerebellar ataxia type 3, psychiatric disorders, substance abuse, and alcohol withdrawal.<sup>1,41</sup> Polysomnographic evaluation demonstrates the presence of non-REM parasomnias and non-REM sleep architecture instability as well as dream enactment behavior in REM sleep with loss of normal REM sleep atonia (showing increased muscle tone during REM sleep).

**Status Dissociatus**

Status dissociatus is a state of complete disintegration of wake/non-REM/REM sleep boundaries that is without identifiable sleep stages and with behavioral and motor manifestations of oneirism (dream-enactment behaviors). An admixture of various polysomnographic markers of different states with unidentifiable sleep staging is noted, with the patient appearing asleep behaviorally but having complex motor behavior typical of dream enactment. The pathophysiologic basis is considered to be related to  $\gamma$ -aminobutyric acid-mediated (GABA-ergic) thalamolimbic dysfunction.<sup>37</sup> Status dissociatus can be seen acutely in alcohol withdrawal, subacutely in autoimmune encephalitis (associated with anti-*N*-methyl-D-aspartate [NMDA] receptor antibodies and anti-voltage-gated potassium channel complex [VGKC] antibodies),<sup>40,42</sup> and on a chronic basis in  $\alpha$ -synuclein neurodegenerative disorders such as Parkinson disease, multiple system atrophy, and dementia with Lewy bodies.

**Agrypnia Excitata**

Agrypnia excitata is an extreme form of status dissociatus, with near-continuous motor and sympathetic hyperactivity, loss of sleep stage N3 (slow-wave) architecture, and dissociation of conventional non-REM sleep markers such as K complexes and sleep spindles. Agrypnia excitata may be seen in asso-

ciation with alcohol withdrawal, Morvan syndrome, or fatal familial insomnia and other prion diseases.<sup>1</sup> These patients exhibit gestures mimicking semi-purposeful tasks in a confused hallucinatory state, termed as *oneiric stupor*, which is the behavioral marker of agrypnia excitata.<sup>40,41</sup>

Careful clinical history with polysomnographic evaluation and diagnostic workup for a possible underlying etiology are warranted. Management includes treating comorbid sleep disorders such as OSA or RLS and optimization of sleep and environmental safety. Clonazepam is the most frequently used agent for this rare parasomnia disorder.<sup>39,40</sup> Alprazolam, temazepam, carbamazepine, and melatonin use have also been reported.<sup>40</sup> For autoimmune etiologies, immunotherapeutic agents such as steroids, IV immunoglobulin (IVIg), and plasma exchange have been used in some cases of status dissociatus associated with autoimmune encephalopathy.<sup>39</sup>

**CONCLUSION**

Non-REM parasomnias include sleep terrors, confusional arousals, and sleepwalking and are most frequent in children and young adults. Non-REM parasomnias are typically benign in most children; therefore, in most cases, parental counseling, education, and watchful waiting can be undertaken. However, in adults, non-REM parasomnias can be potentially injurious, so counseling and education to ensure a safe bedroom environment should be undertaken in all adult patients, and treatment with behavioral therapies (eg, hypnosis) or pharmacotherapy with clonazepam should be considered in cases with significant injury potential. Sexsomnia is less frequently reported but shares a similar pathophysiology. Rare variants of the non-REM parasomnias include overlap parasomnia disorder, status

dissociatus, and agrypnia excitata, and in these cases, underlying etiologies such as neurodegenerative or autoimmune disorders should be sought. Timely recognition and proper management are warranted in all cases to avoid adverse consequences.

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# Circadian Rhythm Sleep-Wake Disorders

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## ABSTRACT

**Purpose of Review:** The endogenous circadian rhythms are one of the cardinal processes that control sleep. They are self-sustaining biological rhythms with a periodicity of approximately 24 hours that may be entrained by external *zeitgebers* (German for time givers), such as light, exercise, and meal times. This article discusses the physiology of the circadian rhythms, their relationship to neurologic disease, and the presentation and treatment of circadian rhythm sleep-wake disorders.

**Recent Findings:** Classic examples of circadian rhythms include cortisol and melatonin secretion, body temperature, and urine volume. More recently, the impact of circadian rhythm on several neurologic disorders has been investigated, such as the timing of occurrence of epileptic seizures as well as neurobehavioral functioning in dementia. Further updates include a more in-depth understanding of the symptoms, consequences, and treatment of circadian sleep-wake disorders, which may occur because of extrinsic misalignment with clock time or because of intrinsic dysfunction of the brain. An example of extrinsic misalignment occurs with jet lag during transmeridian travel or with intrinsic circadian rhythm sleep-wake disorders such as advanced or delayed sleep-wake phase disorders. In advanced sleep-wake phase disorder, which is most common in elderly individuals, sleep onset and morning arousal are undesirably early, leading to impaired evening function with excessive sleepiness and sleep-maintenance insomnia with early morning awakening. By contrast, delayed sleep-wake phase disorder is characterized by an inability to initiate sleep before the early morning hours, with subsequent delayed rise time, leading to clinical symptoms of severe sleep-onset insomnia coupled with excessive daytime sleepiness in the morning hours, as patients are unable to “sleep in” to attain sufficient sleep quantity. Irregular sleep-wake rhythm disorder is misentrainment with patches of brief sleep and wakefulness spread throughout the day, leading to unstable sleep and waking behavioral patterns and an entirely idiosyncratic sleep-wake schedule.

**Summary:** Familiarity with these major circadian rhythm sleep-wake disorder phenotypes and their overlap with other neurologic disorders is essential for the neurologist so that clinicians may intervene and improve patient functioning and quality of life.

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## INTRODUCTION

A natural, endogenous fluctuation is observed in a variety of physiologic functions, the most classic example of which is probably the menstrual cycle. The biological rhythms that have a period of approximately 24 hours are referred to as circadian rhythms.

The term *circadian*, when applied to physiologic or pathophysiologic variations, implies that these rhythms are endogenous and would continue to occur in a similar pattern of approximately 24-hour temporal periodicity in the absence of exogenous factors. Naturally, a tachycardia in response

**KEY POINTS**

- Circadian rhythms are endogenous rhythms that control various physiologic functions and are one of the main factors that control sleep.
- Circadian rhythms have been observed to affect a wide variety of endocrine functions, gastric acid secretion, motor activity pattern, breathing, blood pressure, as well as both normal and abnormal central nervous system activity.

to a 6:00 AM alarm would not be considered a circadian function, although it occurs within a 24-hour period. However, it is often difficult to distinguish whether a 24-hour fluctuation in a specific physiologic function is the result of an endogenous process or of environmental stimuli. Furthermore, most physiologic functions are also affected by the states of sleep and wakefulness, and since sleep typically occurs at night, a nighttime process may be due to either sleep or circadian phase. Some of the early studies on circadian rhythms were conducted in World War II bunkers or deep caves devoid of natural light in an attempt to isolate external influences. Later, two major types of experimental protocols were established to study circadian rhythms.<sup>1</sup> The first protocol is a constant routine, in which the individual is kept in dim light, in one near-constant position, and continuously awake (to eliminate the effect of sleep-wake state) for 24 to 48 hours. This type of protocol has been used to establish the primarily circadian nature of some major functions, such as cortisol secretion, body temperature, urine volume, and melatonin, which have later been used as markers of circadian phase.<sup>2</sup>

The second protocol is forced desynchrony, in which the timing of the sleep period is changed, so that sleep occurs at times that are different from the individual's typical sleep time. The length of the "day" in forced desynchrony is either shorter or longer than 24 hours, while the proportion of scheduled wakefulness and sleep remains 2:1 to allow observance of sleep in all circadian phases. The duration of the episodes varies with the nature of the function studied. Some protocols are ultrashort, with 7 minutes allowed for sleep and 14 minutes of wakefulness (21-minute

"day"), a protocol that was used to determine the "forbidden zone for sleep."<sup>3</sup> Some protocols are ultralong, such as a 42-hour day.<sup>4</sup> In optimal conditions, circadian rhythms are aligned with each other and get re-aligned (entrained) with the social and natural environment. When the endogenous propensity to sleep is misaligned with the needs of the social function, this can lead to inappropriate sleep times and difficulty sleeping (circadian rhythm sleep-wake disorders).

**PHYSIOLOGY OF CIRCADIAN RHYTHMS**

Circadian rhythms have been observed to affect a wide variety of endocrine functions, gastric acid secretion, motor activity pattern,<sup>5,6</sup> breathing,<sup>7</sup> blood pressure,<sup>8</sup> as well as both normal and abnormal central nervous system activity.<sup>9-13</sup> In optimal physiologic conditions, the individually controlled biological rhythms function in synchrony to allow optimal performance.<sup>5</sup> Circadian rhythms would continue to occur with a near 24-hour rhythm even in the absence of external time cues, although the precision of and adaptation to the current environment (entrainment) is ensured through external *zeitgeber* (German for time giver) environmental influences, including ambient light (the most powerful environmental time cue), activity and exercise, and meal times.

**Role in Sleep-Wake Maintenance**

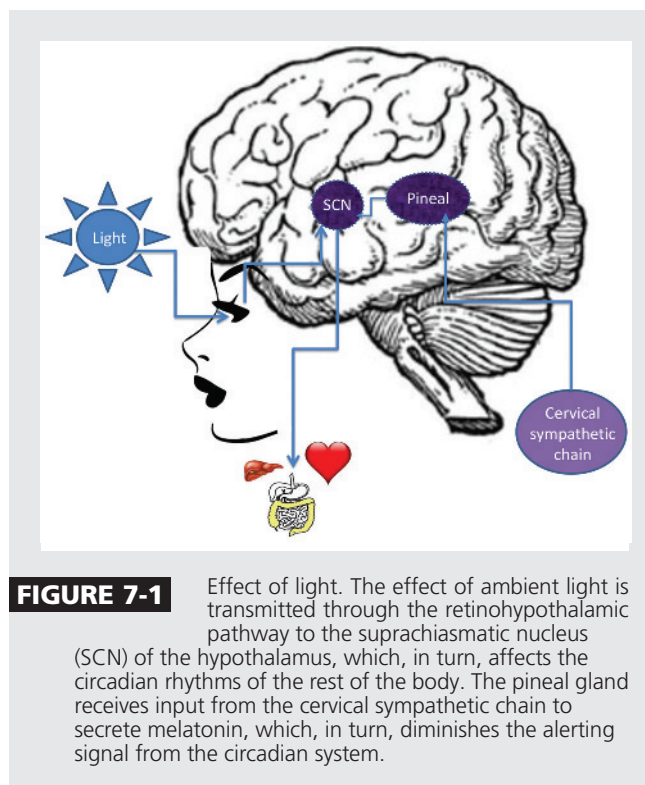
The current model to explain sleep is controlled by two main processes: homeostatic and circadian. The homeostatic process is a longitudinal day-long linear process that increases in strength with the duration of wakefulness and is likely to be mediated by adenosine accumulation through the

period of daytime activity, favoring an increased propensity toward sleep with cumulative wakefulness.<sup>14</sup> The circadian process is primarily an endogenous biological rhythm, which increases in strength with the duration of the biological day, opposing and balancing the effect of the homeostatic drive, thus facilitating continuous wakefulness throughout the day.<sup>5</sup> The same circadian process enables continuous sleep during the main nocturnal sleep period. While the function of circadian rhythms is endogenous and preserved in the absence of any external cues, the timing of the biological day, as noted above, is regulated by multiple exogenous factors such as light, activity and physical exercise, and meal times.

### Effect of Light: Retinohypothalamic Pathway

The effect of circadian rhythm on sleep is regulated by the suprachiasmatic nucleus of the hypothalamus, which receives input via the direct retinohypothalamic pathway. Regular entrainment of the organism with the external environment is facilitated by hypothalamic synchronization of endogenous circadian rhythms with exogenous conditions. Light activation of retinal ganglion cells (which are distinct from the rod and cone cells) is directly conveyed to the hypothalamic suprachiasmatic nucleus via the retinohypothalamic pathway, which then regulates the function of a variety of physiologic functions, including cardiac rhythm, autonomic and endocrine function, and metabolism (Figure 7-1).

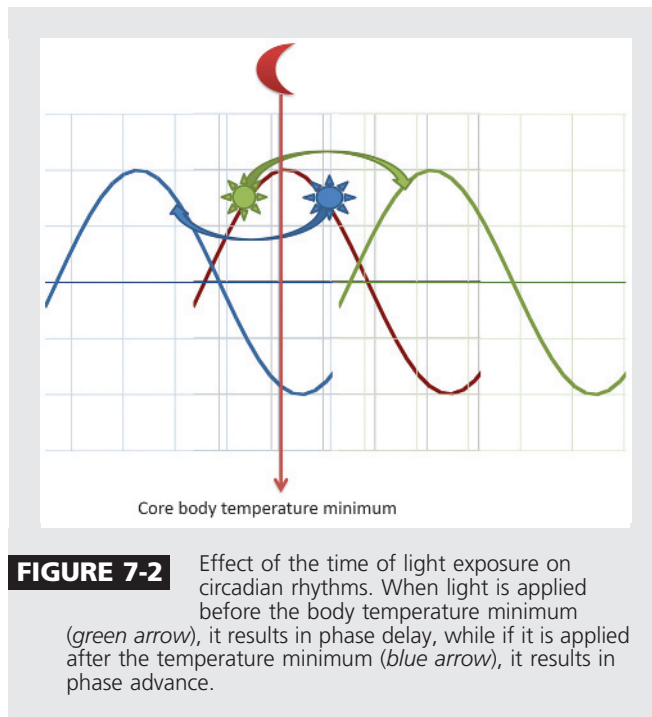
Early studies of circadian rhythms used core body temperature as a marker of circadian phases, with the minimum temperature corresponding to phase 0. Light applied prior to phase 0 delays the circadian phase, while light presented after phase 0 has



a phase-advancing effect (Figure 7-2). The light spectrum,<sup>15,16</sup> as well as timing and length of light exposure,<sup>17</sup> alter the timing of the biological day. In the absence of light, circadian rhythms do not adequately entrain to environmental cues.<sup>18</sup> Diseases that affect light detection, such as macular degeneration, also may impact melatonin production. For example, in a study of patients with age-related macular degeneration, daytime melatonin levels were higher than in controls, suggesting that melatonin secretion was disinhibited, resulting in higher melatonin levels because of less light detection and resultant decreased melatonin suppression by light.<sup>19</sup> Furthermore, in a recent study of 127 blind women, the participants completed an 8-week field study including daily sleep diaries and 4 to 8 hourly urine collections. Most of the participants who had no light perception had an abnormal circadian phase (24%) or were nonentrained

### KEY POINT

■ While the function of circadian rhythms is endogenous and preserved in the absence of any external cues, the timing of the biological day is regulated by multiple exogenous factors such as light, activity and physical exercise, and meal times.

**KEY POINTS**

- During the biological night, melatonin is secreted by the pineal gland. The onset and offset of melatonin secretion are standardly used to determine the timing of an individual's biological night.
- The secretion of melatonin requires integrity of the cervical sympathetic chain. Patients with proximal cervical trauma may have absent melatonin secretion and reduced sleep continuity.
- The frequency of certain physiologic and pathophysiologic events often exhibits a circadian rhythm.

(39%), while less than one-half (37%) were classified as normally entrained. Of the participants with light perception ( $n = 86$ ), the majority were normally entrained (69%).<sup>20</sup>

Circadian variation has been observed in brain network activity. For example, Aeschbach and colleagues<sup>9</sup> studied 19 individuals with “constant routine” conditions and performed analysis of spectral EEG power. They reported two major circadian rhythms of EEG power; the first occurred in the theta band, occurring 1 hour after the onset of melatonin secretion, and the second occurred in the high-frequency alpha band, which had a nadir consistent with the body temperature minimum.

**Role of Melatonin**

During the biological night, melatonin is secreted by the pineal gland. The onset and offset of melatonin secretion are standardly used to determine the timing of an individual's biological night. Since light mediates strong direct suppression of melatonin secre-

tion, melatonin measurements are usually performed in dim light conditions (ideally below 10 lux). Typically, the secretion of melatonin begins approximately 2 hours before the habitual sleep time, reaches peak values, then plateaus during the biological night and decreases sharply after nighttime ends. Melatonin is accepted as one of the most reliable markers of circadian phase and may be measured from plasma, saliva, or urine. The most common circadian function markers are either the onset of melatonin secretion in dim light, referred to as dim light melatonin onset, which occurs 2 to 3 hours before the individual's habitual sleep time; the dim light melatonin offset; and in some situations, the midpoint of melatonin secretion. The primary urinary metabolite of melatonin, 6-sulfatoxymelatonin, collected every 2 to 8 hours over a 24- to 48-hour period, is a practical method to estimate the global timing and amount of melatonin production.<sup>21</sup>

The secretion of melatonin requires integrity of the cervical sympathetic chain. Patients with proximal cervical trauma may have absent melatonin secretion<sup>22</sup> and reduced sleep continuity.<sup>23</sup>

Several genes have been involved in circadian rhythm functions, including *PER1*, *PER2*, and *BMAL1*, and their expression is modulated by melatonin.

**Circadian Vulnerability**

The frequency of certain physiologic and pathophysiologic events often exhibits a circadian rhythm. Clinical examples include many patients with neuropathy who frequently report worsening of pain and somatosensory symptoms in the evening, or the worsening of cognitive and behavioral dysfunction that occurs in many patients with dementia in the evening (sundowning). The frequency



of myocardial infarction is highest in the morning, indicating circadian variation in the frequency of acute myocardial infarction,<sup>24</sup> and sudden cardiac death rates also show a circadian variation.<sup>25</sup> Circadian heart rate variability exhibits a pattern closely corresponding to the frequency of myocardial infarctions.<sup>26</sup> Furthermore, circadian rhythms may be responsible for a morning peak in prothrombotic factors.<sup>27</sup> Circadian peak in plasminogen activator inhibitor-1 occurs at approximately 6:30 AM, the most vulnerable period for adverse cardiovascular events such as heart attacks.

## EPILEPSY

The times when seizures occur may not be random. To date, multiple studies have been conducted on the frequency of seizures, most performed with either continuous video-EEG monitoring or with EEG monitoring at home.<sup>11,28–32</sup> Although some variation exists among studies, the overall findings are relatively similar among different groups and confirm that the time of seizures depends on epileptogenic zone. Temporal lobe seizures are more likely to occur in the afternoon or with a bimodal morning/late afternoon peak,<sup>30,31</sup> while relatively few temporal lobe seizures occur in the nocturnal hours.<sup>32</sup> Frontal lobe seizures are more likely to occur during sleep and in the nocturnal/early morning hours, while, interestingly, parietal seizures peak between 4:00 AM and 7:00 AM, whereas occipital seizures peak in frequency between 4:00 PM and 7:00 PM.<sup>30</sup> Analysis of interictal discharges relative to the circadian phase measured by plasma melatonin in patients with idiopathic generalized epilepsy reveals a trend toward a circadian rhythm pattern; however, the effect of sleep is much stronger, with discharges occurring from sleep more than 8 times as frequently.

These observations concerning the circadian rhythm of various epileptic foci and time of seizure occurrence could potentially be useful for planning therapy. For example, Guilhoto and colleagues<sup>33</sup> administered a higher evening dose of antiepileptic medication in 17 children with nocturnal/early morning seizures, which resulted in a 50% to 90% reduction in seizures. Further studies analyzing chronotherapeutic approaches for epilepsy are needed.

## DEMENTIA

Circadian rhythm dysfunction in dementia has been reported in many studies.<sup>34–36</sup> Patients with dementia who have well-established disruptions of circadian rhythm also have an altered motor activity pattern.<sup>37</sup> This may be due to extension of progressive neurodegeneration to midline brain structures involved in circadian regulation. In a recent study, autopsy results suggest a reduced thickness of the retinal nerve fibers and melanopsin cell loss.<sup>38</sup> Neurodegeneration may also impact the suprachiasmatic nucleus, resulting in circadian rhythm delay and sleep fragmentation.<sup>39</sup>

## DELAYED SLEEP-WAKE PHASE DISORDER

Patients with delayed sleep-wake phase disorder have their natural sleep phase later than required by usual society standards and have difficulty advancing the time of this sleep period. Typically, they present with difficulty waking up in the morning as well as difficulty falling asleep at night. When examined in the absence of time pressures (eg, while on vacation or on weekends), they typically sleep without difficulty, but at a later time (Case 7-1). Table 7-1 lists the *International Classification of Sleep Disorders, Third Edition (ICSD-3)* criteria

## KEY POINTS

- Analysis of interictal discharges relative to circadian phase that are measured by plasma melatonin in patients with idiopathic generalized epilepsy reveals a trend toward a circadian rhythm pattern; however, the effect of sleep is much stronger, with discharges occurring from sleep more than 8 times as frequently.
- Patients with dementia who have well-established disruptions of circadian rhythm also have an altered motor activity pattern. This may be due to extension of progressive neurodegeneration to midline brain structures involved in circadian regulation.



that must be met for a diagnosis of delayed sleep-wake phase disorder.<sup>40</sup>

### Treatment

Three major forms of treatment of delayed sleep-wake phase disorder are available, and these can be used in combination to achieve optimal effect. Melatonin taken prior to bedtime may help with advancing sleep phase; however, the dose and timing is controversial.<sup>41,42</sup> The precise time and dose of the melatonin has varied among studies. Given the physiology of melatonin secretion, if could be argued that, to act as a chronotherapeutic, it should be administered prior to the expected

time of endogenous melatonin secretion (ie, more than 3 hours before the patient's habitual sleep time). One of the earliest studies used a melatonin dose of 5 mg, given 5 hours before the subject's sleep time based on sleep logs.<sup>43</sup> Another landmark study by Munday and colleagues<sup>44</sup> examined the effect of exogenous melatonin at doses of 0.3 mg/d to 3 mg/d, administered between 1.5 and 6.5 hours prior to the subject's bedtime. They found that earlier times of melatonin administration were more effective to advance the time of dim light melatonin onset. However, this has also been a matter of controversy. A recent meta-analysis of

### Case 7-1

A 26-year-old man presented with chronic difficulty with sleep initiation that he had experienced since 14 years of age. He was often awake until 2:00 AM, even if he had been awake since 6:00 AM or 7:00 AM the preceding morning. If uninterrupted, he could sleep until 11:00 AM without any other awakenings and would awaken feeling well refreshed with little daytime sleepiness. He had consistently slept in during the weekends; however, during the week it was necessary to awaken by 6:00 AM for work, and he then experienced significant sleep loss with daytime sleepiness. After he and his wife had started a family, sleeping in was no longer possible. To allow compatibility with his work and family life, he attempted to change his sleep hours to midnight to 8:00 AM. However, he found that even after consistently going to bed at midnight and waking at 8:00 AM, he still was unable to fall asleep before 2:00 AM or later. He did not take naps. His Epworth Sleepiness Scale score was 17 (elevated).

He had tried several treatments to help with sleep initiation in the past, some without medical guidance. These included  $\gamma$ -aminobutyric acid (GABA) and thiamine, diphenhydramine, trazodone, and melatonin, but none of these were successful. Treatment with ramelteon 8 mg, taken before the desired bedtime (11:00 PM), was initiated at his first visit in the sleep clinic. At his 3-month follow-up visit, he reported a significant improvement and could keep a regular schedule compatible with his work and family life.

**Comment.** This case illustrates a typical presentation of delayed sleep-wake phase disorder. Patients are often misdiagnosed as having insomnia and are often unsuccessfully treated with hypnotics or are sometimes self-medicated with various health supplements, while the more crucial issue of sleep timing is ignored. Further worsening due to superimposed anxiety and maladaptive sleep-related behaviors is commonly seen in clinical practice. Explanation of the role of the circadian rhythms and, in appropriate situations, use of melatonin or melatonin agonists may be helpful, as in this case.

**TABLE 7-1 Diagnostic Criteria for Delayed Sleep-Wake Phase Disorder<sup>a</sup>**

- A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of the inability to fall asleep and difficulty awakening at a desired or required clock time.
- B. The symptoms are present for at least 3 months.
- C. When patients are allowed to choose their *ad libitum* schedule, they will exhibit improved sleep quality and duration and maintain a delayed phase of the 24-hour sleep-wake pattern.
- D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
- E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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**KEY POINT**

■ Three major forms of treatment of delayed sleep-wake phase disorder are available, and these can be used in combination to achieve optimal effect: hypnotic medications, light therapy, and chronotherapy.

available placebo-controlled studies on the efficacy of exogenous melatonin for delayed sleep-wake phase disorder found no definite difference of effect size relative to the timing of melatonin administration.<sup>42</sup>

As seen in **Case 7-1**, use of a hypnotic medication may help with sleep initiation, and in this case, ramelteon, a melatonin receptor agonist, was most helpful. Light therapy can help by providing an important signal that suppresses melatonin secretion, thus signaling the onset of the biological day. Either full-spectrum bright light can be used, generally at 2500 lux or brighter intensity for 20 to 30 minutes upon awakening, although recently, blue light has been shown to have a more powerful effect.<sup>45</sup> While timing the light exposure, light administered prior to the biological midnight (the time of dim light melatonin onset) will delay rather than advance the sleep phase. Typical duration of light exposure in the morning is 20 to 30 minutes, and since measurement of melatonin is not usually available in the clinical

setting, bright light exposure at the time of habitual awakening is generally recommended. Potential side effects include eye strain, headaches, and, rarely, mania in predisposed patients with nonseasonal depression.

Chronotherapy by schedule shifting is based on the assumption that phase delay is generally easier and better tolerated than phase advancement and consists of recommending a rapid scheduled progressive delay of the bed-time over a period of approximately 1 to 2 weeks. Since this approach necessarily leads to scheduling sleep at times that are inconsistent with work and social obligations, it is often found impractical by many patients as it requires prescribed “off time” from work or school during its application (**Table 7-2**).<sup>46</sup>

**Wake-promoting agents.** Some attention has been given to vitamin B<sub>12</sub>. In a multicenter study of patients with delayed sleep-wake phase disorder ( $n = 50$ , with a mean age of 26.8 years  $\pm$  1.3 years), participants received a 3 mg total daily dose of oral vitamin B<sub>12</sub> (3 times daily divided dosing) versus

**KEY POINT**

■ Non-24-hour sleep-wake disorder is a sleep-wake rhythm disorder affecting the normal entrainment and synchronization of the patient to a 24-hour circadian rhythm.

**TABLE 7-2 Melatonin Agonists**

Medication	Dose	Indications	Cautions
Ramelteon	8 mg/d	Insomnia	Generally well tolerated, main side effects are dizziness and drowsiness
Tasimelteon	20 mg/d	Non-24-hour sleep-wake disorder	Drowsiness, nightmares, headaches
Melatonin	0.5–6 mg/d	Used in insomnia and circadian rhythm disorders, as well as in other conditions (eg, rapid eye movement sleep behavior disorder) <sup>a</sup>	Dizziness, somnolence, headaches

<sup>a</sup> All listed indications for melatonin are off label (not approved by the US Food and Drug Administration [FDA]).

placebo (double blinded) for a period of 4 weeks. No major side effects occurred, but improvements were relatively modest.<sup>47</sup>

Often, a combination of light therapy and melatonin is used. In one study, melatonin was administered 5.75 hours prior to the habitual sleep time, and a 3-hour bright light of 3000 lux was administered, starting 1 hour prior to habitual wake time.<sup>48</sup> The combination of bright light plus melatonin was more effective than either one alone.

### ADVANCED SLEEP-WAKE PHASE DISORDER

Patients with advanced sleep-wake phase disorder have their natural sleep phase earlier than usual society norms but, distinct from delayed sleep-wake phase disorder, these patients present with insomnia in the early morning with the inability to maintain sleep, with sleepiness occurring in the early evening or even late afternoon hours (**Case 7-2**). **Table 7-3** lists the *ICSD-3* criteria that must be met for a diagnosis of advanced sleep-wake phase disorder.<sup>40</sup>

### Treatment

Similar to delayed sleep-wake phase disorder, advanced sleep-wake phase disorder can be treated effectively with appropriately timed light exposure. Since, in this case, the goal is to delay the sleep phase, the light should be administered in the late afternoon or early evening hours.

### NON-24-HOUR SLEEP-WAKE DISORDER

Non-24-hour sleep-wake disorder is a sleep-wake rhythm disorder affecting the normal entrainment and synchronization of the patient to a 24-hour circadian rhythm. The basis for non-24-hour sleep-wake disorder is that the actual intrinsic biological circadian period length for most individuals is actually longer than 24 hours at close to 24.2 hours. In normal individuals, the strong *zeitgeber* of light input to the suprachiasmatic nucleus enables the hypothalamus to synchronize the individual's internal time period, resulting in entrainment to the shorter 24-hour clock day length. However, in individuals who are completely blind, resulting from bilateral loss of functioning photosensitive

## Case 7-2

A 67-year-old man presented to the sleep clinic with inappropriate sleepiness in the early evening hours and difficulties with sleep maintenance. He described that he often fell asleep around 5:00 PM or 6:00 PM and was unable to either socialize with friends or have conversations with his wife in the evening. Repeatedly, he went to bed immediately after dinner, slept until 3:00 AM, and then he woke up and was unable to fall back asleep. Multiple hypnotic medication trials had been unsuccessful.

He was diagnosed with advanced sleep-wake phase disorder and treated with bright light therapy daily at 4:00 PM, reporting thereafter that he was then able to converse with his wife nightly after dinner for a few hours before bedtime at 8:30 PM, when he fell asleep promptly and awakened in the morning at 5:00 AM, which was considerably more desirable for him.

**Comment.** This case is an example of advanced sleep-wake phase disorder, contributing to treatment-resistant insomnia. Light treatment was helpful in alleviating his symptoms.

retinal ganglion cells, retinas, or optic nerves, the retinohypothalamic tract is severed, resulting in a complete absence of light input to the suprachiasmatic nucleus and a “free-running” circadian behavioral pattern in which the patient’s intrinsically longer circadian period length is misaligned to the clock day, causing the affected individ-

ual to shift to a slightly later bed and rise time each day and to be unable to align to any usual clock time. Even more rarely, non-24-hour sleep-wake disorder may occur in sighted individuals for unclear reasons, probably due to an abnormally long intrinsic circadian rhythm. The clinical result is a combination of insomnia and often daytime

**TABLE 7-3 Diagnostic Criteria for Advanced Sleep-Wake Phase Disorder<sup>a</sup>**

- A. There is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening.
- B. Symptoms are present for at least 3 months.
- C. When patients are allowed to sleep in accordance with their internal biological clock, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode.
- D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
- E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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# KEY POINT

■ Patients with irregular sleep-wake rhythm disorder have difficulty synchronizing the time for sleep with societal norms for sleep times, and, as a result, they sleep during irregular periods during the day or night.

hypersomnolence if the individual is not allowed to remain on his or her free-running sleep-wake schedule and is forced to adopt to a conventional day-time schedule (similar to that seen in delayed sleep-wake rhythm disorder).

Non-24-hour sleep-wake disorder is extremely difficult to treat. In sighted individuals, application of morning bright light exposure and early evening melatonin, similar to the approach used in delayed sleep-wake rhythm disorder, may be attempted. In completely blind individuals, the recently approved medication tasimelteon (20 mg each night taken at bedtime), a nonselective melatonin receptor agonist, improved entrainment as well as sleep initiation and maintenance.<sup>49</sup> However, the expense of this medication has been a significant practical barrier to its adoption in mainstream clinical use.

## IRREGULAR SLEEP-WAKE RHYTHM DISORDER

Patients with irregular sleep-wake rhythm disorder have difficulty synchronizing the time for sleep with societal norms for sleep times, and, as a result, they sleep during irregular periods during the day or night. Table 7-4 lists

the *ICSD-3* criteria that must be met for a diagnosis of irregular sleep-wake rhythm disorder.<sup>40</sup>

Irregular sleep-wake rhythm disorder is more commonly observed in neurodegenerative disorders, such as dementia. Sleep and wake episodes across the 24-hour cycle are fragmented, with the longest sleep period being typically fewer than 4 hours. Individuals or caregivers report frequent cat naps throughout the daytime. Total sleep time across the 24 hours may be normal for age.

Older adults with Alzheimer disease who experience sundowning may represent a clinical subtype with more severe sleep fragmentation and lower circadian rhythm amplitude than those who do not experience sundowning.

**Treatment.** Treatment of irregular sleep-wake rhythm disorder involves a structured environment with timed light exposure in the morning hours. Caution should be used when sedatives are administered for treatment.<sup>50</sup>

## CONCLUSION

The endogenous circadian rhythms play a major role in the regulation of

**TABLE 7-4** Diagnostic Criteria for Irregular Sleep-Wake Rhythm Disorder<sup>a</sup>

- A. The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both.
- B. Symptoms are present for at least 3 months.
- C. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate no major sleep period and multiple irregular sleep bouts with at least three brief sleep periods during a 24-hour period.
- D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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multiple physiologic functions, including sleep and wakefulness. Many neurologic disorders, such as epilepsy, are affected by the circadian system. Disorders of the circadian rhythm often manifest as poor sleep. Patients with delayed sleep-wake phase disorder have late sleep onset, often misinterpreted as insomnia, while in advanced sleep-wake phase disorder, patients have inappropriately early sleep onset and early awakening. With some neurodegenerative conditions, the ability to maintain a regular sleep-wake schedule is impaired and can lead to irregular sleep-wake rhythm disorder, while the absence of light perception can lead to a non-24-hour sleep-wake disorder. Understanding circadian rhythms is essential for appropriate treatment of sleep disorders.

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Drs Avidan and Neubauer discuss the off-label uses of various central nervous system-acting medications for insomnia, which include sedating antidepressants such as amitriptyline, doxepin, mirtazapine, and trazodone; the antipsychotic quetiapine; antihistamine compounds such as doxylamine; medications available over-the-counter marketed as sleep aids as single compounds or as a combination therapy with analgesics (acetaminophen or ibuprofen); and dietary supplement sleep aids such as chamomile, hops, kava kava, melatonin, passionflower, tart cherry juice, and valerian.

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# Chronic Insomnia Disorder

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## ABSTRACT

**Purpose of Review:** Neurologists, along with all health care providers, commonly encounter patients with insomnia, which is a condition that impacts patients' underlying neurologic conditions in a bidirectional manner. While chronic insomnia is one of the most common sleep disturbances, only a small proportion of individuals with this condition discuss their sleep problems with their providers. When insomnia is described, it is more often in relationship to another medical problem, as opposed to an independent condition. In neurology practice, multiple factors including pain, movement disorders, sleep apnea, and medications that act on the central nervous system often contribute to insomnia. An all-inclusive approach is necessary when evaluating sleep problems in patients with insomnia.

**Recent Findings:** The US Food and Drug Administration (FDA) has approved several medications for the treatment of insomnia that target specific receptor systems in the brain and incorporate several unique pharmacodynamic and pharmacokinetic profiles that can represent customized therapy for specific insomnia phenotypes. FDA-approved medications for insomnia include  $\gamma$ -aminobutyric acid (GABA)-modulating benzodiazepine receptor agonists, a melatonin receptor agonist, a histamine receptor antagonist, and the newest approved option, a hypocretin (orexin) receptor antagonist.

**Summary:** This article provides an evidence-based multidisciplinary approach to the treatment of insomnia, highlighting the rationale and utility of cognitive-behavioral therapy and pharmacologic interventions. Neurologists should be proactive in assessing the impact of underlying comorbidities on insomnia, particularly in the setting of psychiatric conditions such as depression, sleep disorders such as circadian rhythm disorders, and medical problems such as nocturia.

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## INTRODUCTION

Insomnia is pervasive in neurology practice, but is often undiagnosed and untreated. Specific patient cohorts such as older adults, patients who live in nursing homes, and individuals with underlying chronic comorbid medical, neurologic, and psychiatric disorders are particularly at risk. These patients often present with difficulties falling asleep and maintaining sleep and experience significant daytime consequences such as fatigue, memory problems, and poor psychosocial function.

Chronic insomnia disorder is among the most widely reported clinical con-

ditions in medicine and has a significant impact on populations treated in neurology practices.<sup>1,2</sup> Sleep difficulties often result from multiple etiologies and may require a multidisciplinary treatment approach based on established evaluation guidelines and evidence-based therapies.<sup>3</sup> Recent evidence demonstrates that poor sleep is associated with a wide range of negative health outcomes and that poorer quality of life and medical, neurologic, and psychiatric comorbidities disrupt sleep. Given this bidirectionality, neurologists should take measures to discuss sleep problems and their impact on the

underlying neurologic disease and take specific steps toward enhancing sleep quantity and quality in their patients. By doing so, the clinician may have a broader role in promoting wellness and bringing about improvements in some comorbid conditions as well.

## DEFINITION OF INSOMNIA

Insomnia disorder refers to persistent difficulties falling asleep, maintaining sleep, or waking up earlier than habitual rise time and is associated with impairment of daytime functioning despite the opportunity for sufficient sleep duration.<sup>4</sup> Although patients with insomnia report the chronicity of wakefulness during the night, insomnia disorder is conceptualized to represent a 24-hour condition reflecting a state of hyperarousal leading to both the nighttime and daytime symptomatology.<sup>5</sup>

Several classification systems offer criteria for insomnia nosologies and specific insomnia phenotypes. Insomnia classification schemes are outlined by the *International Classification of Diseases, Tenth Revision (ICD-10)* and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, which is the American Psychiatric Association's 2013 update to its classification and diagnostic tool.<sup>6,7</sup> Both the *ICD-10* and *DSM-5* assimilate categorizations of key sleep disorders including various insomnia subtypes. The 2014 American Academy of Sleep Medicine (AASM) *International Classification of Sleep Disorders, Third Edition (ICSD-3)* defines general criteria for chronic insomnia disorder, reviewed in **Table 8-1**, as well as short-term insomnia disorder.<sup>4</sup> The chronic and short-term insomnia disorder criteria

## KEY POINTS

- Recent evidence demonstrates that poor sleep is associated with a wide range of negative health outcomes and that poorer quality of life and medical, neurologic, and psychiatric comorbidities disrupt sleep.
- Insomnia disorder refers to persistent difficulties falling asleep, maintaining sleep, or waking up earlier than habitual rise time and is associated with impairment of daytime functioning despite the opportunity for sufficient sleep duration.

**TABLE 8-1** Diagnostic Criteria for Chronic Insomnia Disorder<sup>a</sup>

**Criteria A through F are required for a diagnosis of chronic insomnia disorder**

- A. The patient/family members/caregiver reports or observes one or more of the following
  - 1. Difficulties with sleep initiation
  - 2. Difficulties with sleep maintenance
  - 3. Waking up earlier than desired with difficulties reinitiating sleep
  - 4. Opposition to going to bed during habitual bedtime schedule
  - 5. Difficulties sleeping without the intervention of the parent or caregiver
- B. The patient/patient's parent/caregiver report or observe one or more of the following difficulties in relationship to the nighttime sleep difficulty
  - 1. Malaise/fatigue
  - 2. Impairment in concentration, attention, or memory
  - 3. Impairment in domains of social function, fulfillment of family duties, or difficulties with occupational or academic performance
  - 4. Disturbances in mood and/or irritability
  - 5. Excessive daytime somnolence
  - 6. Problems with behavioral function (eg, aggression, hyperactivity, impulsivity)
  - 7. Impairment in motivation/energy/initiative
  - 8. Proneness for accidents and/or errors
  - 9. Concerns about or dissatisfaction with sleep quality

*Continued on page 1066*



**TABLE 8-1** **Diagnostic Criteria for Chronic Insomnia Disorder<sup>a</sup>***Continued from page 1065*

- C. The reported sleep/wake difficulties cannot be otherwise explained by inadequate opportunity or inadequate circumstances for sleep (ie, the patients should have sufficient allotted time for sleep and environmental conditions are conducive for sleep [safe, dark, quiet, and comfortable]).
- D. Frequency criteria: The sleep difficulties and associated daytime symptoms must occur at a frequency of at least 3 times per week.
- E. Duration criteria: The sleep disturbance and the associated daytime symptoms must be present at least 3 months.
- F. The sleep/wake disturbance is not attributed to or explained by another underlying primary sleep disorder (such as obstructive sleep apnea, circadian rhythm sleep-wake disorder, or a motor disorder of sleep).

**Notes**

1. Insomnia may be observed across all age groups. Opposition to going to bed on a proper schedule and difficulty sleeping without a parent or in the absence of a caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to a significant disturbance in cognitive or functional impairment (eg, patients with underlying neurodegenerative diseases such as Alzheimer dementia).
2. A unique circumstance occurs when patients suffer from insomnia and experience recurrent episodes of sleep/wake difficulties lasting several weeks at a time interval persisting for several years, but may not meet the specific duration criteria (listed in E) for any single such episode. These patients should be assigned a diagnosis of chronic insomnia disorder, given the persistence of their intermittent sleep difficulties over time.
3. Patients with chronic insomnia treated with hypnotic medications may improve and thus not meet the criteria for an insomnia disorder while using these agents. In the absence of hypnotics, however, this patient population may meet the diagnostic criteria for insomnia disorder, especially if they express concerns about their dissatisfaction with sleep continuity in the absence of hypnotics.
4. Neurologic, medical, psychiatric, and primary sleep comorbidities such as chronic pain disorders, Parkinson disease, and restless legs syndrome may induce sleep/wake complaints suggestive of insomnia. A distinct diagnosis of insomnia may not apply when these disturbances are suspected to be underlying inducers of the sleep difficulty. In many patients, however, these conditions are chronic and may not be exclusive causes of sleep difficulty. A decision to adjudicate a unique insomnia diagnosis considers: "How much of the time does the sleep difficulty arise specifically as a result of factors directly attributable to the medical/psychiatric/neurologic/sleep comorbidity?" or "Are there specific conditions or settings during which the sleep/wake complaints occur in the absence of these factors?" "Have perpetuating behavioral or cognitive issues (eg, negative expectations, conditioned arousal, and sleep-disruptive habits) arisen, indicative of an autonomous aspect occurring in parallel, but independent of the underlying insomnia?" A distinct diagnosis of chronic insomnia disorder may be established if there is sufficient ground to suspect that the patient's sleep/wake complaints are not distinctly induced by the medical comorbidity. If this is indeed the case, then those sleep/wake complaints could merit the separate need to evaluate the potential for therapeutic interventions.

<sup>a</sup> Modified with permission from the American Academy of Sleep Medicine.<sup>4</sup>  
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are similar, with key difference being the duration (fewer than 3 months for short-term insomnia disorder and 3 months or more for chronic insomnia disorder).

The *ICSD-3* insomnia classification requires components of both nighttime and daytime elements.<sup>4</sup> The nighttime sleep symptoms consist of (1) difficulty falling asleep, (2) difficulty maintaining sleep, or (3) early morning awakening despite sufficient sleep opportunity. Subjective problems reported by patients may include a pattern of delayed sleep onset, many brief or protracted awakenings, and a sensation that sleep is fragmented and very light. The most likely motivation prompting patients with insomnia to seek medical attention is related to concerns about daytime consequences. The spectrum of these daytime symptoms varies and may include poor concentration, attention, cognition, and motivation; fatigue; depressed mood; irritability; decreased energy; and a predilection to make errors.

While patients with chronic insomnia tend to worry about their inability to sleep well and the negative impact this has on their lives, they often do not describe excessive daytime sleepiness. In fact, the opposite often is observed; they report abnormal wakefulness during the day and night, which could be the manifestation of their underlying hyperarousal process. A common daytime complaint is feeling “tired and wired.”

## EPIDEMIOLOGY

The prevalence of insomnia varies significantly depending on age, gender, comorbidities, and the specific population cohorts being examined.<sup>1</sup> However, women and older adults tend to express a higher risk for insomnia. In the general population, about one-third of adults report inter-

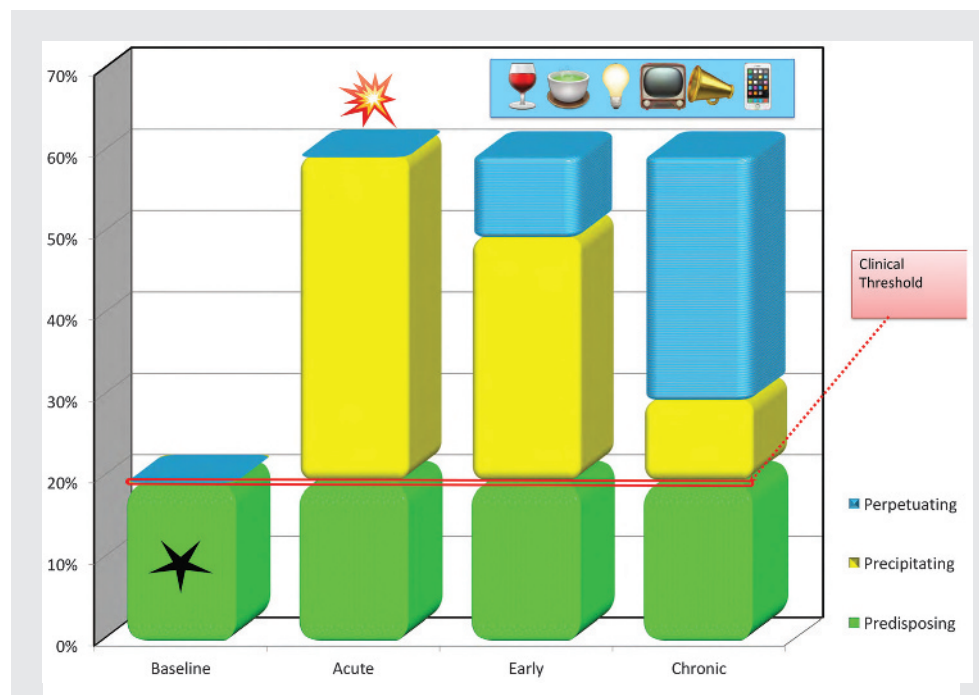
mittent symptoms of insomnia, while about 10% meet the criteria for chronic insomnia disorder associated with daytime sequelae. It is common for brief insomnia episodes to have identifiable precipitants, such as situational crises, a new medication (eg, steroids for multiple sclerosis exacerbation), acute schedule changes (eg, neurology resident on call), or an acute neurologic problem (eg, new stroke requiring intensive care admission).

## EVOLUTION OF ACUTE TO CHRONIC INSOMNIA

Several models provide a rationale for the transformation from acute to chronic insomnia. The 3P model describes how chronic insomnia develops as a consequence of underlying *predisposing* features, *precipitating* factors, and *perpetuating* processes. Together these three components elevate a person's insomnia risk above a clinical threshold, as demonstrated in **Figure 8-1**.<sup>8</sup> The figure provides a representation of Spielman and colleagues<sup>8</sup> 3P model of chronic insomnia etiology. Everyone has a predetermined risk or a baseline degree of vulnerability for insomnia due to genetics or personality phenotypes. People who do not express sleep disturbance at their baseline would be below the level of clinically significant insomnia (**Figure 8-1**). Acute stressors may raise patients beyond the theoretical clinical insomnia threshold to a point where they develop insomnia symptoms. Over time, perpetuating factors (eg, chronic habitual behaviors such as lying awake in bed, caffeine, alcohol, daytime napping, or nighttime light from television, phone, or other electronic devices) ultimately promote persistent and pervasive insomnia symptoms, which are responsible for propagation of the sleep disturbance. Cognitive-behavioral therapy for insomnia

## KEY POINTS

- The insomnia classification by the *International Classification of Sleep Disorders, Third Edition* requires components of both nighttime and daytime elements.
- While patients with chronic insomnia tend to worry about their inability to sleep well and the negative impact this has on their lives, they often do not describe excessive daytime sleepiness.
- In the general population, about one-third of adults report intermittent symptoms of insomnia, while about 10% meet the criteria for chronic insomnia associated with daytime sequelae.
- The 3P model shows how chronic insomnia develops as a consequence of the underlying predisposing features, precipitating factors, and perpetuating processes.

**FIGURE 8-1**

3P model of insomnia etiology.<sup>8</sup> The 3P (*predisposing*, *precipitating*, and *perpetuating*) model of insomnia etiology explains that all people express a certain vulnerability for insomnia (*predisposing* factors). Insomnia disorder occurs when a *precipitating* event pushes patients above the insomnia threshold. When the precipitating factor diminishes, the insomnia is kept above the threshold when patients develop behaviorally conditioned arousal responses associated with the bedroom environment and maladaptive behaviors that perpetuate the insomnia. These *perpetuating* factors are shown in the figure as use of alcohol too close to bedtime, caffeine too late during the day, and excessive light and use of television and light-emitting electronic devices. People who do not express sleep disturbance at their baseline would be below the level of clinically significant insomnia (as demarcated by the *black star* within the baseline period).

Modified with permission from Spielman AJ, Glovinsky P, Plenum Press.<sup>8</sup> © 1991 Springer Science and Business Media.

(CBT-I) and pharmacotherapy addresses this third and final *P* as patients move across a continuum from acute to chronic insomnia.

### CHRONIC INSOMNIA

For many neurology patients, insomnia is very likely to become a chronic nightly problem that persists for a few weeks, months, and even years, although various temporal patterns are possible. Patients may present with intermittent episodes of insomnia lasting weeks to months interspersed with relatively normal sleep, or they may have recurrent and intermittent sleep problems lasting from several

nights each week or each month. Insomnia may be described as primary insomnia and conceptualized as an independent disorder when no concomitant conditions that seem to be contributing to the sleep disturbance are present. In contrast, a patient with sleep difficulty presumably influenced by the presence of another disorder, such as major depression, fibromyalgia, substance abuse, or obstructive sleep apnea, may be viewed as having a comorbid type of insomnia. Circadian rhythm disorders can also present with chronic insomnia. Older age is associated with alteration in circadian rhythmicity of sleep with predisposition

for phase advancement of sleep timing, referred to as advanced sleep-wake phase disorder.<sup>9,10</sup> Patients with Alzheimer disease frequently develop irregular sleep rhythms with difficulty staying asleep for consolidated periods of time, long awakenings at night, and daytime sleepiness requiring frequent naps.

The *ICSD-3* does not differentiate primary from comorbid insomnia given that no apparent biological factors discriminate between possible insomnia subtypes, although previous *ICSD* versions incorporated conceptually useful descriptive subtypes with psychophysiologic, paradoxical, and idiopathic insomnias as examples of primary insomnia.<sup>4</sup> According to the *ICSD-3* nosology, patients meeting a general insomnia criteria then could be diagnosed with a specific insomnia disorder, including the following subtypes.<sup>4</sup>

### **Psychophysiologic Insomnia**

The underlying mechanism of psychophysiologic insomnia is a behaviorally based phenotype reflecting a conditioned heightened arousal associated with the bed, the environment within the bedroom (ie, clock), and maladaptive bedtime routines. Excessive focus on and worry about sleep, and elevated levels of cognitive and somatic arousal, particularly at bedtime, are common. Learned sleep-preventing associations perpetuate the sleep difficulty and promote this chronic form of insomnia (**Case 8-1**).

### **Adjustment Insomnia**

Adjustment insomnia occurs in temporal association with an identifiable stressor usually spanning a duration of fewer than 3 months. Sleep should improve with the resolution of the stressor. In some cases, adjustment insomnia may evolve into a chronic form and warrant a new insomnia diagnosis. The *ICSD-3*

categorizes this as short-term insomnia as long as the symptoms are present for fewer than 3 months.<sup>4</sup>

### **Paradoxical Insomnia**

Paradoxical insomnia was previously referred to as sleep state misperception and reflects a complaint of severe sleep disturbance in the absence of corroborative and objectively verifiable indicators of the degree of sleep disturbance claimed by the patient. For example, a major mismatch may occur between a patient's misperception of complete sleeplessness during a night of in-laboratory polysomnography that objectively records a total sleep time of 6 hours.

### **Idiopathic Insomnia**

This subtype reflects persistent insomnia unrelated to an identifiable precipitant that begins insidiously in childhood and continues chronically in an unremitting pattern into adulthood. While no consistent genetic biomarkers or neural pathology have been described in these patients, idiopathic insomnia is thought to arise from either genetically based or congenital alterations in the sleep-inducing or wake-promoting systems in the brain.

### **Inadequate Sleep Hygiene**

Patients with this insomnia subtype engage in maladaptive behaviors that interfere with normal sleep promotion or continuity. These detrimental behaviors may include aberrant sleep-wake schedule problems, consumption or use of substances likely to disrupt sleep (eg, caffeine, tobacco, or alcohol), and engaging in evening routines that are not conducive to sleep. Other practices that promote this insomnia subtype include prolonged daytime napping that is too close to bedtime, regularly using the bedroom for activities other than sleep, participating in stimulating or emotionally upsetting

#### **KEY POINT**

■ The underlying mechanism of psychophysiologic insomnia is a behaviorally based phenotype reflecting a conditioned heightened arousal associated with the bed, the environment within the bedroom (ie, clock), and maladaptive bedtime routines.

### Case 8-1

A 62-year-old man presented to the neurology clinic complaining of insomnia that had begun 2 years ago when he had failed to obtain funding to support his research as a physics professor. He brought his sleep log to the appointment, which revealed prolonged sleep latency and that he had resorted to watching television and using alcohol to help initiate sleep. He noted that stress or sleeping in unfamiliar surroundings exacerbated his sleep problems. He reported working on his laptop until he went to bed at 10:00 PM, when he would start reading the news and doing puzzles on his tablet device in bed, until he eventually felt sleepy around midnight. His sleep diary also revealed that he resorted to drinking two to three shots of vodka to help him relax and induce sleep. He denied snoring or apneic spells and did not feel “restless” or have an urge to move his legs. He denied using caffeine and did not use any medications on a daily or nightly basis. He had no chronic health issues.

His body mass index was 26.5 kg/m<sup>2</sup>. His physical and neurologic examination was normal, and his upper airway examination was completely normal and was not crowded.

The patient was diagnosed with psychophysiologic insomnia. He wished to avoid any pharmacotherapy, but he expressed an interest in conservative behavioral management. He was referred for cognitive-behavioral therapy for insomnia, and he was informed that mentally alerting activities, such as doing puzzles on the tablet device in bed, should be avoided, as well as limiting light sources at night to a minimum level. He was also asked to avoid the use of alcohol before bedtime. After 6 weeks of treatment, he returned to clinic reporting that his symptoms had improved. He was able to sleep for 7 hours per night without interruption and did not need to rely on any agents to induce sleep.

**Comment.** This patient’s history and physical examination did not point to a primary medical, psychiatric, or sleep disorder and was most consistent with psychophysiologic insomnia, which is characterized by difficulties falling asleep at the desired bedtime, mental hyperarousal in bed, or heightened somatic tension interfering with sleep onset. In addition to cognitive-behavioral therapy for insomnia, appropriate nonpharmacologic suggestions for improving sleep hygiene include avoidance of mentally distracting activities, which can improve anxiety levels and keep hyperarousal from interfering with sleep onset. Another suggestion for improving sleep hygiene is to avoid spending time in bed awake and to read relaxing (or even boring) books. The light source should be limited to a small bedside lamp or book light and set ideally at the minimum level needed to allow undemanding reading. Patients should also avoid the use of alcohol before bedtime because of its adverse impact on sleep architecture.

activities too close to bedtime, or failing to maintain a comfortable environment for sleep.<sup>4</sup> A significant degree of overlap exists between inadequate sleep hygiene and other forms of insomnia, with most patients with insomnia admitting to at least one of these common maladaptive sleep be-

haviors that are targetable by cognitive-behavioral therapy interventions.

### **Behavioral Insomnia of Childhood**

Behavioral insomnia of childhood is a diagnosis reserved for sleep difficulties in pediatric patients and incorporates



the following three sleep-onset association and limit-setting subtypes:

- The sleep-onset association type reflects the child's dependency on a specific activity/behavior/stimulation, typically objects or settings, for initiating sleep or returning to sleep following an awakening. When these are absent, sleep onset is significantly delayed.
- The limit-setting type is demarcated by behaviors of stalling or refusing going to bed that are attributable to an inadequate limit setting by the parent or caregiver.
- The mixed hybrid type is characterized by features of both sleep-onset association difficulties and bedtime resistance.

### **Insomnia Due to a Mental Disorder and Insomnia Due to a Medical Condition**

Diagnoses of insomnia due to a mental disorder or insomnia due to a medical condition presume the presence of comorbid psychiatric and medical conditions with a clear temporal association with the underlying sleep disturbance and generally are used where the insomnia is severe enough to warrant independent treatment.

### **Insomnia Due to a Drug or Substance**

Insomnia due to a drug or substance represents sleep problems clearly and temporally associated with the drug or substance intoxication or withdrawal from a wide range of medications.

## **EVALUATION AND ASSESSMENT OF INSOMNIA**

A good general rule in the assessment of insomnia is to consider the potential etiology and likely factors that may predispose the patient to develop sleep difficulty, precipitate an insom-

nia episode over the clinical threshold, and perpetuate the insomnia symptoms over time once the precipitant diminishes (**Figure 8-1**).<sup>3,11</sup>

The clinical guidelines for evaluating insomnia published by the AASM in 2008 highlight the key steps of the historical inventory during the clinical interview, focusing on the specific sleep-related symptoms as well as the potential contributions of psychiatric, medical, and substance use disorders.<sup>3</sup> When possible, a bed partner or other family member should be interviewed to provide detailed information about any apneic spells, snoring, abnormal sleep-related movements, leg jerks, dream enactment, or behavioral abnormalities.<sup>3</sup>

Sleep questionnaires and sleep logs are very important in supplementing the formal evaluation of a patient with insomnia. A sleep diary spanning a period of several weeks can be quite helpful in highlighting patterns of sleep disturbance and uncovering potential circadian rhythm sleep-wake disorders. An example of a sleep diary may be downloaded from the AASM website ([yoursleep.aasmnet.org/pdf/sleepdiary.pdf](http://yoursleep.aasmnet.org/pdf/sleepdiary.pdf)). A recently developed consensus sleep diary provides a standardized patient-informed sleep diary in the assessment of insomnia based on expert consensus.<sup>12</sup>

Neurologists should conduct a general physical and neurologic examination, a dedicated sleep medicine examination, and a baseline mental status examination. Polysomnography may be reserved for patients suspected of having a concomitant sleep disorder (eg, sleep-disordered breathing or periodic limb movement disorder) that is likely contributing to the insomnia symptoms, but it should not be ordered routinely in the absence of these suspected sleep-disturbing symptoms. Home sleep apnea testing is reserved

## **KEY POINTS**

- A good general rule in the assessment of insomnia is to consider the potential etiology and likely factors that may predispose the patient to develop sleep difficulty, precipitate an insomnia episode over the clinical threshold, and perpetuate the insomnia symptoms over time once the precipitant diminishes.
- When possible, a bed partner or other family member should be interviewed to provide detailed information about any apneic spells, snoring, abnormal sleep-related movements, leg jerks, dream enactment, or behavioral abnormalities.
- Sleep questionnaires and sleep logs are very important in supplementing the formal evaluation of a patient with insomnia.

**KEY POINT**

■ The diversity of influences on sleep and wakefulness, extensive variability in patient expectations, along with the wide spectrum of insomnia phenotypes highlights the view that a unitary treatment pathway is not always possible.

for patients likely to be experiencing sleep apnea. The clinician should be aware of the specific contraindications for home sleep apnea testing, which are likely to contribute to insomnia (ie, movement disorders of sleep).<sup>13,14</sup> For more information on home sleep apnea testing, refer to the article “Sleep-Disordered Breathing” by Nancy R. Foldvary-Schaefer, DO, MS, and Tina E. Waters, MD,<sup>15</sup> in this issue of *Continuum*.

The core elements of a sleep history should focus on the specific chronicity of insomnia symptoms, impact on daytime activities and functioning, contribution of sleep-wake schedule routines, and other sleep-related symptoms (eg, snoring, movements, behaviors). **Table 8-2** provides an inventory of questions for interviewing patients presenting with insomnia.

**MANAGEMENT OF INSOMNIA**

Chronic insomnia is complex and often challenging, but can be very

rewarding to patients, bed partners, family members, and providers when successfully managed. Chronic insomnia may result from the interplay of numerous processes frequently occurring simultaneously. Successful intervention requires a multidisciplinary treatment philosophy incorporating several concurrent strategies and, in some cases, a staged approach that may involve further testing.<sup>3</sup>

**General Recommendations**

The diversity of influences on sleep and wakefulness, extensive variability in patient expectations, along with the wide spectrum of insomnia phenotypes highlights the view that a unitary treatment pathway is not always possible. The fundamental key to managing patients with insomnia is to creatively customize therapy for individual patients. Clinicians managing insomnia should remember to spend sufficient time collecting the sleep history, appreciate specific patient

**TABLE 8-2** Insomnia Inventory Questionnaire

1. How long have you had symptoms of insomnia?
2. Was there a specific trigger?
3. What is the timing of the insomnia symptoms during the night?
4. Please estimate the time of sleep onset and total sleep times and the frequency and character of awakenings.
5. What is the typical rise time?
6. Is the difficulty primarily sleep onset or sleep maintenance, or is it a combination of the two?
7. Describe your evening routines and your bedroom setting.
8. Are there apparent situational or environmental variables?
9. Are you taking medications or using substances specifically for sleep? Are any of these temporally related to worsening of or improvement of sleep?
10. Describe your previous sleep difficulty and the results of any treatment approaches.
11. What specific hypnotics (if any) have you tried? (List name of medication, date of use, dose, instructions given, duration, impact, results, and side effects, if any.)
12. Have you tried cognitive-behavioral therapy? If yes, please describe.

expectations, and collaborate with patients in setting clear treatment goals specific to their nighttime and daytime symptoms. Any patient provided with hypnotics should be monitored prospectively for therapeutic progress and potential. A history of possible treatment-related adverse effects such as complex nocturnal behaviors, amnesic sleep eating, or depressed mood should be sought by the prescribing physician, who should then recalibrate the therapeutic plan as needed.

## Insomnia and its Comorbidities

When managing chronic insomnia in the neurology outpatient setting, clinicians must consider the specific underlying neurologic and psychosocial comorbid conditions, as illustrated in **Figure 8-2**. A successful outcome is possible when these conditions (eg, pain syndrome, epilepsy, Parkinson disease, and mental health disorders such as anxiety and depression) are appropriately addressed.

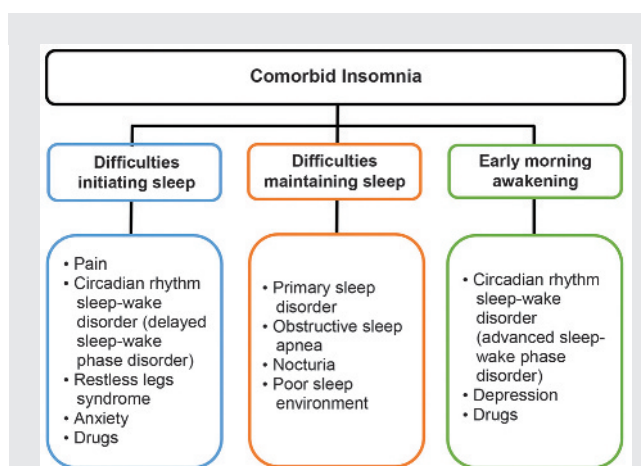
As part of the initial assessment of insomnia, neurologists should attempt

to identify and treat other sleep disorders that may lead to insomnia. Examples of factors that contribute to difficulty initiating sleep include anxiety, excessive caffeine use, and symptoms of restless legs syndrome (RLS). An example of RLS contributing to sleep initiation insomnia is illustrated in **Figure 8-3**.

As shown in **Figure 8-2**, other comorbidities likely to manifest with insomnia include circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder, manifesting with early bedtime and early morning awakenings, and delayed sleep-wake phase disorder, resulting in difficulties initiating sleep and difficulty awakening before late morning or early afternoon. Sleep apnea may contribute to sleep maintenance insomnia, especially with more advanced stages of Parkinson disease, where nocturia is very common, making the condition difficult to treat. Periodic limb movement disorder may also lead to significant insomnia, especially in patients with pain syndromes, Parkinson disease, narcolepsy,

## KEY POINTS

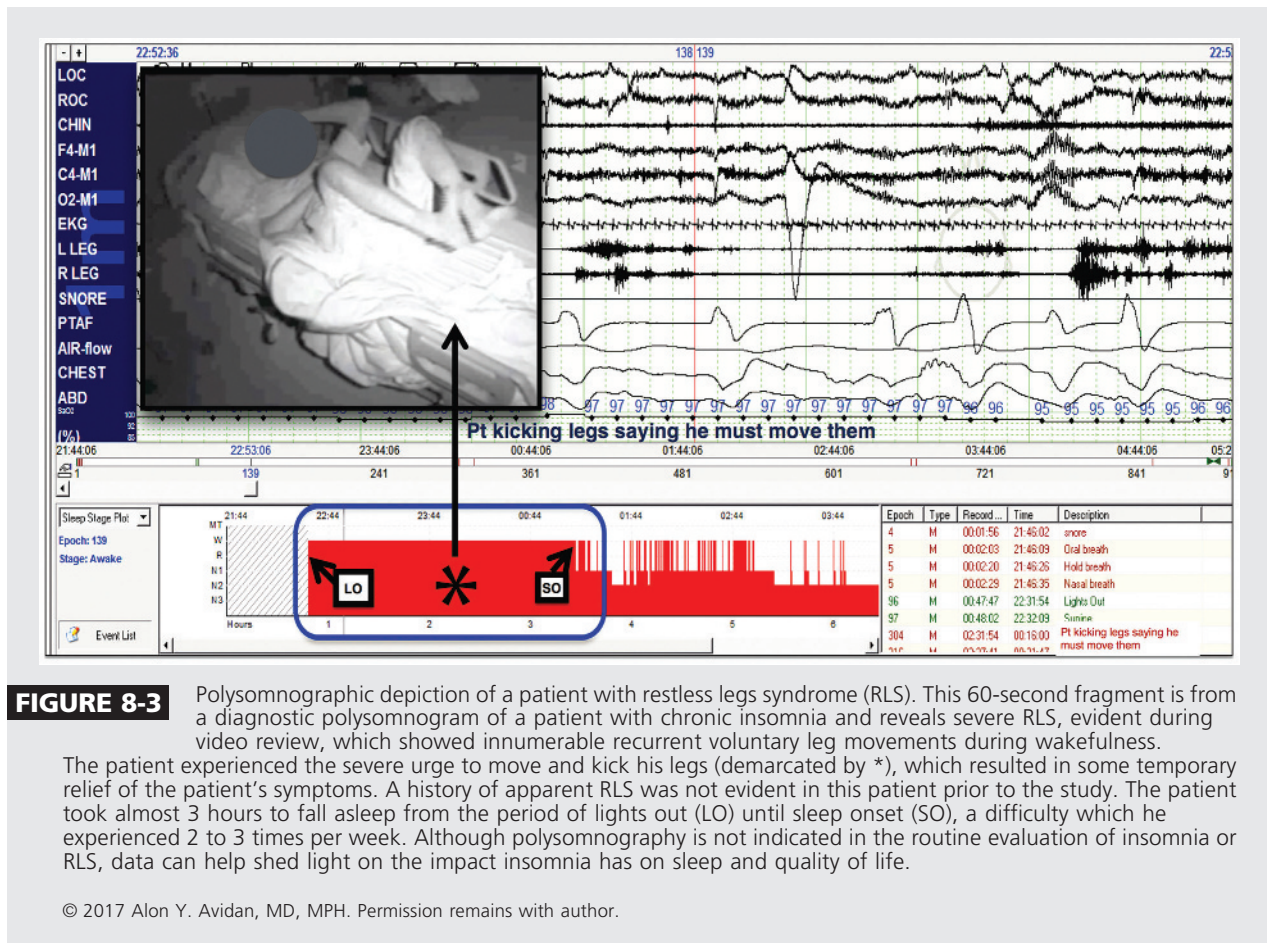
- When managing chronic insomnia in the neurology outpatient setting, clinicians must consider the specific underlying neurologic and psychosocial comorbid conditions.
- As part of the initial assessment of insomnia, neurologists should attempt to identify and treat other sleep disorders that may lead to insomnia.
- Other comorbidities likely to manifest with insomnia include circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder, manifesting with early bedtime and early morning awakenings, and delayed sleep-wake phase disorder, resulting in difficulties initiating sleep and difficulty awakening before late morning or early afternoon.



**FIGURE 8-2**

Differential diagnosis of insomnia according to its manner of occurrence during the night. The flow diagram depicts etiologic considerations in patients presenting with sleep initiation insomnia, sleep maintenance insomnia, and early morning awakenings.

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# KEY POINT

■ When managing insomnia, the initial approach should consider the potential influence of intrinsic (patient-related) and extrinsic (environmental) factors, the latter including noise, temperature, light, radio, or television.

and multiple sclerosis. Early morning awakening also may be a sign of a mood disorder. The bidirectional relationship between pain, motor disorders of sleep, as well as psychiatric conditions such as depression and anxiety, as illustrated in **Figure 8-4**, is well established in the literature. Insomnia and poor sleep contribute to worsened pain, anxiety, and depression, which, in turn, worsen the underlying sleep disturbances.<sup>16–18</sup> Interestingly, unhealthy behaviors are also associated with insomnia symptoms in a bidirectional manner; insomnia is associated with heavy drinking and physical inactivity, which are also associated with poorer sleep and insomnia symptoms.<sup>19</sup>

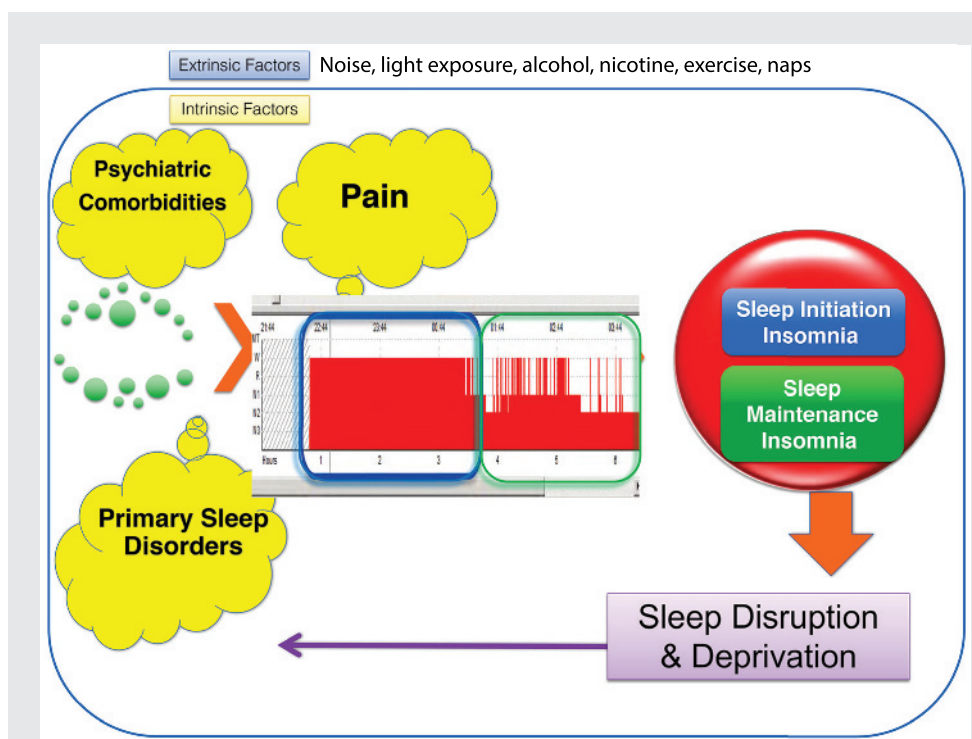
When managing insomnia, the initial approach should consider the

potential influence of intrinsic (patient-related) and extrinsic (environmental) factors, the latter including noise, temperature, light, radio, or television, as shown in **Figure 8-4**. These factors should be targeted for patient education and correction during CBT-I. One key item with significant relevance in neurology is the use of medications, particularly antidepressants, stimulants, wake-promoting agents, antiepileptic drugs, and dopamine agonists and antagonists. Neurologists should work closely with primary care physicians and psychiatrists to provide treatment regarding timing and dosages with the lowest potential to impact sleep onset or maintenance. Good general advice for patients with insomnia is to avoid all stimulating drugs and substances (eg,



#### KEY POINT

■ Sleep hygiene education is a good starting point for all patients who present with chronic insomnia because it sets the fundamental ground rules that help eradicate persistent sleep difficulty.



**FIGURE 8-4**

Mechanism of and contribution of key comorbidities to the perpetuation of chronic insomnia. Specific intrinsic (patient-related) factors are illustrated, depicting how their bidirectional relationship with insomnia worsens insomnia. Insomnia, when poorly treated, often worsens the comorbidities (eg, pain, depression). Extrinsic factors include excessive noise, light exposure, alcohol at bedtime, nicotine, exercise, and long naps too close to bedtime.

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stimulating/alerting antidepressants and antiepileptic drugs, bronchodilators, thyroid hormones, corticosteroids, decongestants, caffeine after lunchtime, nicotine, and evening alcohol) or, when certain activating/alerting prescription drugs are necessary, to time administration earlier in the daytime with avoidance of nighttime dosing whenever possible. When possible, sedating medications (particularly antiepileptic drugs, anxiolytics, and benzodiazepine modulators) should be taken close to bedtime. However, caution should be taken toward possible influences of medications on sleep architecture, alteration, and suppression of upper airway muscle tone, and whether medications may precipitate or exacerbate RLS.

### Education and Healthy Sleep Habits

An inventory of healthy sleep behaviors for review with all patients who present with insomnia is provided in **Table 8-3**.<sup>20</sup> Sleep hygiene education is a good starting point for all patients who present with chronic insomnia because it sets the fundamental ground rules that help eradicate persistent sleep difficulty. Treatment usually starts with educating patients about the basic processes that impact sleep and mechanisms to optimize the functioning of the existing physiologic mechanisms that regulate the sleep-wake cycle.<sup>3</sup>

**Ensure sleep-wake timing is regular.** Patients need to maintain regularity in their sleep and wake times and



**TABLE 8-3 Healthy Sleep Habits<sup>a</sup>****► Healthy Sleep Habits at Night**

Dedicate at least 30 minutes of wind-down time before bedtime in which you do something relaxing, such as read a book. Dim the lights in the house slightly for an hour or so before bed.

Disconnect electronics: Stay away from light-emitting devices such as television, laptops, phones, and tablets, as the blue light from their screens can alert the brain and make it harder to fall asleep.

Use the bed and bedroom for sleep and sex only.

Establish a regular prebedtime routine and a regular sleep-wake schedule.

Avoid alcohol or heavy meals too close to bedtime.

Create a sleep-promoting environment that is dark, cool, and comfortable.

Avoid disturbing noises: Consider a bedside fan or white-noise machine to block out disturbing sounds.

If unable to fall asleep within 20 minutes, get up and return to another space in the house to engage in a relaxing activity, such as reading or listening to music. Lying in bed awake can create an unhealthy conditioned association between your sleeping environment and wakefulness. You want your bed to conjure sleepy thoughts and positive feelings only.

Go to bed and wake up at the same time every day. Even if you have difficulties falling asleep and trouble awakening in the morning because you are tired, try to get up at the same time (weekends included).

This can help adjust your body's clock and aid in falling asleep at night.

**► Healthy Sleep Habits During the Day**

Avoid caffeine, particularly after noon.

Avoid alcohol and nicotine, especially close to bedtime.

Exercise regularly earlier during the day, but not within 3 hours before bedtime.

Avoid naps, particularly longer than 20 minutes and outside the 1:00 PM to 3:00 PM time window.

Keep a sleep diary to identify sleep habits and patterns that you can share with your doctor.

<sup>a</sup> Data from the National Sleep Foundation.<sup>20</sup> [sleepfoundation.org/insomnia/content/what-do-when-you-cant-sleep](http://sleepfoundation.org/insomnia/content/what-do-when-you-cant-sleep).

should allocate sufficient opportunity for adequate sleep duration.

**Avoid excessive time awake in bed.** Spending habitual time awake in the bed has the potential to perpetuate the behavioral conditioned association of the bedroom environment with insomnia, which reinforces hyperarousal. The patient should be educated to leave the bed after 15 to 20 sleepless minutes, getting up to pursue a quiet

distracting activity (while avoiding work activities, light exposure, or electronic devices) in another room of the home until feeling sleepy enough to return to the bedroom so that the desired association between the bed and sleep is reestablished.

**Refrain from inappropriate and excessive napping behavior.** For some people, routine regular daytime napping may be appropriate, but for

patients with insomnia, naps should be discouraged, especially in the late afternoon or evening. Prolonged napping too close to the evening could facilitate sleep-onset difficulties. If the patient has difficulty refraining from napping, restricting naps to no longer than a 15- to 20-minute period earlier in the afternoon and, if necessary, setting alarms to limit the nap duration should be suggested.

**Encourage environmental conditions conducive to sleep.** A relaxing evening and bedtime routine should facilitate sleep onset. Work projects, watching television late in the evening, and computer-related activities should be strictly minimized within 2 hours of bedtime. Inappropriate evening light exposure and device screen time (eg, laptops, video game devices, tablets, and phones) can induce a circadian phase delay that undermines the initiation of sleep at the desired time.

**Minimize noise.** The sleep environment should be free of disturbing

noises. White noise-generating devices may be beneficial.

**Set a cooler room temperature.** To optimize sleep, the ideal temperature should be neutral to slightly cool, as sleep onset is typically associated with the body's temperature nadir point in the evening.

### Psychological and Behavioral Strategies

A wide variety of well-defined behavioral approaches have been shown to be effective in treating patients with insomnia.<sup>21</sup> While some patients have an expectation that their insomnia management would include a hypnotic medication, data demonstrate that the ideal strategy is one that specifically incorporates CBT-I.<sup>22</sup>

The core elements of CBT-I are outlined in **Table 8-4** and attend to components that regulate the circadian cycle, which include the underlying psychological processes that can impact sleep and the maladaptive cognitive distortions that fuel the perpetuation

#### KEY POINTS

- While some patients have an expectation that their insomnia management would include a hypnotic medication, data demonstrate that the ideal strategy is one that specifically incorporates cognitive-behavioral therapy for insomnia.
- The core elements of cognitive-behavioral therapy for insomnia attend to components that regulate the circadian cycle, which include the underlying psychological processes that can impact sleep and the maladaptive cognitive distortions that fuel the perpetuation of insomnia.

**TABLE 8-4 Techniques and Special Goals Outlined During Cognitive-Behavioral Therapy Sessions**

Technique	Goal
Sleep restriction	Restrict actual time spent in bed to enhance and increase the homeostatic drive for sleep, enhance sleep depth and consolidation, improve sleep onset and maintenance
Stimulus control therapy	Associate behaviors conducive to sleep with the activity of falling asleep, imprint bed and bedroom as sleep stimulus
Cognitive therapy	Address dysfunctional beliefs and attitudes about sleep
Relaxation training	Decrease psychological and cognitive hyperarousal and anxiety
Circadian rhythm entrainment	Reinforce or reset biological rhythm using light and/or chronotherapy
Cognitive-behavior therapy	Combination of behavioral and cognitive approaches listed above

of insomnia. CBT-I assimilates specific recommendations that facilitate healthy sleep routines, specifically, bedtime, time in bed, advice on when to attempt to sleep, and individualized cognitive psychotherapy to limit the maladaptive beliefs and assumptions regarding sleep and insomnia from hindering future progress. CBT-I provided as either a short-term or sustained therapy has excellent merit.<sup>23</sup> The basic components of CBT-I consist of a cognitive component and at least one behavioral element, such as stimulus control therapy or sleep restriction therapy. While CBT-I has been investigated primarily as a formalized approach over a series of sessions, studies have reported the benefits of streamlined and more flexible schedules, including online CBT-I for those without access to a provider in their area, limited insurance coverage, or a work/personal schedule that does not allow participation in in-person CBT-I sessions.<sup>24–27</sup>

**Sleep restriction.** The goal of sleep restriction therapy is to increase the homeostatic drive for sleep to promote improved sleep onset and maintenance by reducing excessive wakefulness in bed.<sup>11</sup> Less wakeful time in bed also should limit the continued reinforcement between being in bed and being awake. This treatment initially curtails patients' time in bed to the amount of sleep they report being able to achieve. Typically, the time in bed is not reduced to fewer than 5 hours. Patients are required to maintain sleep diaries throughout the therapy and work closely with the CBT-I therapist. The morning rise time is kept consistent throughout the therapy to allow the patient to benefit from morning light exposure and to entrain (resynchronize) the existing sleep-wake cycle with the circadian system and photoperiod.

**Stimulus control therapy.** The aim of stimulus control therapy is to assist

patients in imprinting the activity and behavior of going to bed with falling asleep. It requires them to ensure a regular morning wake-up time and avoid daytime napping.<sup>28</sup> The therapy assumes that patients with chronic insomnia have incorrectly assimilated maladaptive bedtime and bedroom routines. These activities promote wakefulness through cognitive conditioning, which is reinforced over time as patients remain awake in bed, become frustrated, and experience mental hyperarousal. Patients participating in stimulus control therapy are instructed to go to bed and attempt sleep when they feel sleepy and able to fall asleep. If sleep fails to occur in 10 minutes, they are instructed to get out of bed and move to another room, repeating the process as needed.

**Relaxation therapy.** Relaxation therapy attempts to decrease anxiety and tension while awake in bed. Specific relaxation techniques may include progressive relaxation, abdominal breathing, guided imagery, yoga, and meditation.

### **Pharmacologic Approaches**

Medical management of insomnia consists of four main treatment categories: (1) medications approved by the US Food and Drug Administration (FDA) for the treatment of insomnia, (2) sedating prescription medications not specifically approved by the FDA for insomnia treatment, (3) over-the-counter sleep aids that are regulated by the FDA but do not require a prescription, and (4) an extensive list of unregulated dietary supplements that are commercially available, with claims of sleep benefits.

Additionally, people often attempt to treat their insomnia with alcohol, although this strategy is rarely recommended. The sedating effect of alcohol may promote a shorter sleep

onset, but subsequent sleep quality typically is poor, with increased arousals later during the night and ultimately with a net negative effect.

**Insomnia medications approved by the US Food and Drug Administration.** Pharmacotherapy for insomnia that is approved by the FDA consists of agents with four distinct mechanisms of actions:  $\gamma$ -aminobutyric acid A (GABA-A) receptor modulation, melatonin receptor agonism, histamine 1 ( $H_1$ ) receptor antagonism, and hypocretin/orexin antagonism. These agents have distinct advantages in that both efficacy and safety have been studied with appropriate doses in unique populations of patients with insomnia.<sup>29</sup> **Table 8-5** outlines the commonly used hypnotics based on the mechanism of action, pharmacodynamic profile (sleep onset, sleep maintenance, or difficulties re-initiating sleep following an awakening), available doses, approximate elimination half-lives, specific FDA indication, Drug Enforcement Administration schedule, and pregnancy category for each of these medications. The following sections describe the major pharmacodynamic categories of insomnia medications.

**Benzodiazepine receptor modulation.** GABA is the principal inhibitory neurotransmitter in the central nervous system, and its receptors are defined structurally and pharmacologically as GABA-A and GABA-B. GABA-A receptors are associated with a central chloride channel ionophore, as illustrated in **Figure 8-5**.<sup>32</sup> The benzodiazepine and nonbenzodiazepine receptor agonist hypnotics are allosteric modulators of GABA responses at the GABA-A receptor complex, a pentameric transmembrane protein consisting of five subunits (two  $\alpha$ , two  $\beta$ , and one  $\gamma$ ) that form a rosette around the chloride channel, as illustrated in **Figure 8-5**. Activation of GABA-A re-

ceptors by GABA through its binding at the  $\alpha$ - $\beta$  subunit interface opens the chloride channel, leading to an immediate and substantial rise in chloride conductance across the cell membrane, rendering the neuron unable to raise an action potential, which leads to phasic inhibition of the neuron. The result is membrane hyperpolarization, which induces neural inhibition.<sup>33,34</sup> Traditional benzodiazepine hypnotics (ie, temazepam, triazolam) do not differentiate among GABA-A receptor subtypes. The nonbenzodiazepine receptor agonist hypnotics zolpidem and zaleplon act on the  $\alpha_1$ GABA-A receptor subtypes, which mediate sedation, while eszopiclone preferentially targets the  $\alpha_3$ GABA-A receptor subtype predominantly in the reticular nucleus of the thalamus.

All GABA-A benzodiazepine receptor modulators interact with binding sites with different affinities to the various subunits, which accounts for some of the variation in their pharmacologic responses. The very broad distribution of GABA-A receptors suggests that the benzodiazepine hypnotic action may induce a widespread brain effect depending on the site of action.<sup>35</sup> The benzodiazepine hypnotics are generally well tolerated, but because the distribution of GABA-A receptors is widespread, the side effect profile is more extensive, ranging from drowsiness, dizziness, headache, and lightheadedness to ataxia and complex nocturnal behaviors, such as amnesic sleep-related eating and anterograde amnesia.<sup>29</sup> Patients using these agents may be more likely to report rebound insomnia on abrupt discontinuation following chronic use. These medications are associated with an abuse potential and therefore are designated by the Drug Enforcement Agency as Schedule IV medications. Benzodiazepine hypnotics are Pregnancy Category X

## KEY POINTS

- Pharmacotherapy for insomnia that is approved by the US Food and Drug Administration consists of agents with four distinct mechanisms of actions:  $\gamma$ -aminobutyric acid A receptor modulation, melatonin receptor agonism, histamine 1 receptor antagonism, and hypocretin/orexin antagonism.
- The benzodiazepine hypnotics are generally well tolerated, but because the distribution of  $\gamma$ -aminobutyric acid A receptors is widespread, the side effect profile is more extensive, ranging from drowsiness, dizziness, headache, and lightheadedness to ataxia and complex nocturnal behaviors, such as amnesic sleep-related eating and anterograde amnesia.

**TABLE 8-5** Insomnia Medications Approved by the US Food and Drug Administration<sup>a</sup>

Medication <sup>b</sup>	Available Formulations	Half-life	Indications
<b>Benzodiazepine immediate release</b>			
Flurazepam	15 mg, 30 mg	48–120 hours	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings
Temazepam	7.5 mg, 15 mg, 22.5 mg, 30 mg	8–20 hours	Short-term treatment of insomnia
Triazolam	0.125 mg, 0.25 mg	2–4 hours	Short-term treatment of insomnia
Quazepam	7.5 mg, 15 mg	48–120 hours	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings
Estazolam	1 mg, 2 mg	8–24 hours	Short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings; administered at bedtime; improved sleep induction and sleep maintenance
<b>Nonbenzodiazepine immediate release</b>			
Zolpidem	5 mg, 10 mg (recommended maximum dose of 5 mg for women)	1.5–2.4 hours	Short-term treatment of insomnia characterized by difficulties with sleep initiation
Zaleplon	5 mg, 10 mg	1 hour	Short-term treatment of insomnia, shown to decrease the time to sleep onset
Eszopiclone	1 mg, 2 mg, 3 mg	5–7 hours	Treatment of insomnia, administered at bedtime; decreased sleep latency and improved sleep maintenance
<b>Nonbenzodiazepine extended release</b>			
Zolpidem extended release	6.25 mg, 12.5 mg (recommended maximum dose of 6.25 mg for women)	2.8–2.9 hours	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset)

and nonbenzodiazepines are Pregnancy Category C.

Benzodiazepine and nonbenzodiazepine receptor agonist hypnotics are available in various pharmacologic

formulations: immediate release oral spray, sublingual dissolvable alternative delivery formulations, and an extended-release tablet. All benzodiazepine receptor agonist hypnotics are



Most Common Side Effects	Drug Enforcement Administration Class <sup>c</sup>	Pregnancy Category <sup>d</sup>
Dizziness, drowsiness, lightheadedness, staggering, loss of coordination, falling	IV	X
Drowsiness, dizziness, lightheadedness, difficulty with coordination	IV	X
Drowsiness, headache, dizziness, lightheadedness, pins and needles feelings on the skin, difficulty with coordination	IV	X
Drowsiness, headache	IV	X
Somnolence, hypokinesia, dizziness, abnormal coordination	IV	X
Drowsiness, dizziness, diarrhea, drugged feeling	IV	C
Drowsiness, lightheadedness, dizziness, pins and needles feeling on the skin, difficulty with coordination	IV	C
Unpleasant taste in mouth, dry mouth, drowsiness, dizziness, headache, symptoms of the common cold	IV	C
Headache, sleepiness, dizziness	IV	C

*Continued on page 1082*

formulated for bedtime use with one exception; the lower-dose dissolvable formulation is indicated for middle-of-the-night insomnia provided that 4 hours of sleep time are available.

With the exception of eszopiclone and zolpidem extended release, for which no limitation on the duration of use is implied, the formal indications for the benzodiazepine receptor agonist

**TABLE 8-5** **Insomnia Medications Approved by the US Food and Drug Administration<sup>a</sup>***Continued from page 1081*

Medication <sup>b</sup>	Available Formulations	Half-life	Indications
<b>Nonbenzodiazepine alternative delivery</b>			
Zolpidem oral spray	5 mg, 10 mg	Approximately 2.5 hours	Short-term treatment of insomnia characterized by difficulties with sleep initiation
Zolpidem sublingual	5 mg, 10 mg	Approximately 2.5 hours	Short-term treatment of insomnia characterized by difficulties with sleep initiation
	1.75 mg, 3.5 mg	Approximately 2.5 hours	As needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep, provided that 4 hours of sleep time remain
<b>Selective melatonin receptor agonist</b>			
Ramelteon	8 mg	1–2.6 hours	Treatment of insomnia characterized by difficulty with sleep onset
<b>Selective histamine 1 receptor antagonist</b>			
Doxepin	3 mg, 6 mg	15.3 hours	Treatment of insomnia characterized by difficulties with sleep maintenance
<b>Hypocretin (orexin) receptor antagonist</b>			
Suvorexant	5 mg, 10 mg, 15 mg, 20 mg	12 hours	Treatment of insomnia, characterized by difficulties with sleep onset or sleep maintenance

<sup>a</sup> Table current as of June 25, 2017.<sup>b</sup> The authors advise readers to review the most current package inserts for each medication listed given that updates are highly dynamic and variable.<sup>c</sup> Drug Enforcement Administration Class IV refers to a lower abuse potential than schedule III drugs and limited physical and/or psychological dependence.<sup>30</sup><sup>d</sup> Pregnancy medication Category X refers to studies in animals or human beings that have demonstrated fetal abnormalities or where there is evidence of fetal risk. The drug is contraindicated in women who are or may become pregnant. Pregnancy medication Category C refers to animal studies that have shown risk to the fetus but where there are no controlled studies in women, or where studies in women and animals are not available.<sup>31</sup> A new US Food and Drug Administration (FDA) pregnancy and lactation labeling rule went into effect on June 30, 2015; however, the timelines for implementing this new labeling information on drug labels and package inserts are variable. All listed pregnancy category information uses past FDA pregnancy labeling practices, as labels and package inserts for some medications have not yet been updated.

hypnotics specify that they are intended for short-term therapy.

**Melatonin receptor agonism.** A single melatonin receptor agonist, ramelteon, is approved by the FDA for treating insomnia. A second agonist, tasimelteon, is now approved by the FDA for the treatment of non-24-hour sleep-wake disorder. Ramelteon is specifically indicated for the management of insomnia characterized by sleep initiation difficulties. Ramelteon is available at a single dose of 8 mg, which is

indicated for all patient subgroups including women and adults older than age 65. Specific contraindications include the clinical setting of severe hepatic disease or in patients concomitantly taking fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) indicated for obsessive-compulsive disorder that is a potent CYP1A2 inhibitor (a key ramelteon metabolic pathway). Drowsiness, tiredness, and dizziness are the most common side effects. Ramelteon has no abuse

Most Common Side Effects	Drug Enforcement Administration Class <sup>c</sup>	Pregnancy Category <sup>d</sup>
Drowsiness, dizziness, diarrhea, drugged feeling	IV	C
Drowsiness, dizziness, diarrhea, drugged feeling	IV	C
Headache, nausea, fatigue	IV	C
Drowsiness, tiredness, dizziness	None	C
Somnolence/sedation, nausea, upper respiratory tract infection	None	C
Somnolence, depression, rare but possible risk of rapid eye movement (REM) intrusion phenomena	IV	C

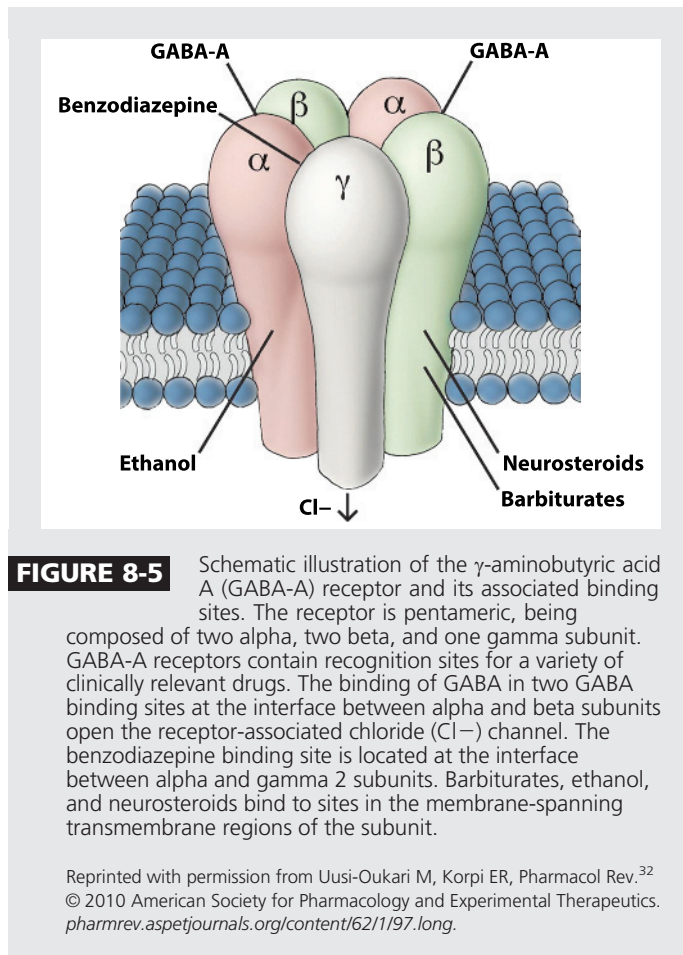
potential; hence, it is considered a nonscheduled medication and is classed as Pregnancy Category C.

As a selective agonist of the melatonin types 1 and 2 (MT<sub>1</sub> and MT<sub>2</sub>) receptors, ramelteon binds to these receptors with selectivity. These MT receptors are expressed with a high density in the suprachiasmatic nucleus of the anterior hypothalamus.<sup>36</sup> Melatonin is produced by the pineal gland in a process regulated by the circadian system. Melatonin exerts its activity by

attenuating the suprachiasmatic nucleus wake-promoting effects as opposed to actively promoting sleep (**Figure 8-6**). In this model, secretion of melatonin in the evening coincides with the peak of the suprachiasmatic nucleus-driven arousal cycle, ultimately inhibiting the mechanisms that promote evening wakefulness (**Figure 8-6B**). The presence of melatonin, in turn, reduces the circadian wakeful drive and facilitates activation of the sleep-promoting brain structures.<sup>2</sup>

#### KEY POINT

■ Melatonin exerts its activity by attenuating the suprachiasmatic nucleus wake-promoting effects as opposed to actively promoting sleep.

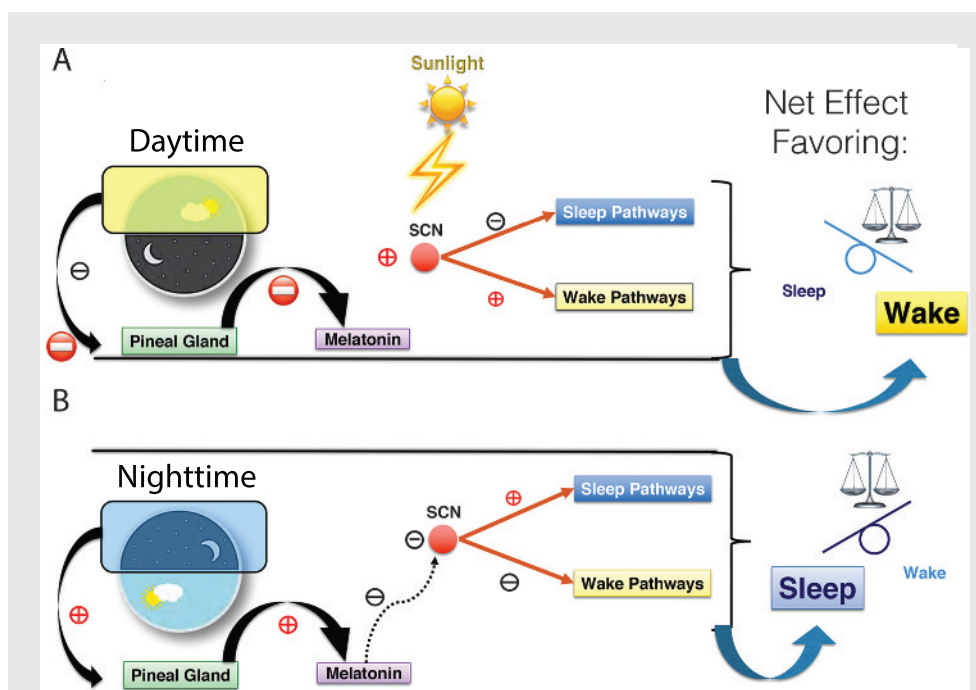
**KEY POINT**

- Compared with other histaminergic compounds, ultra-low-dose doxepin is unusual for its very high specificity and selectivity for histamine 1 receptor antagonist activity.

The evening melatonin rise and  $\text{MT}_1$  agonist action decreases the suprachiasmatic nucleus-driven wake-promoting stimulation that is present during the latter hours of the wake period and thereby facilitates bedtime sleep onset, as illustrated in **Figure 8-6**. The  $\text{MT}_2$  action promotes a circadian resynchronizing effect that reinforces the circadian timing and allows for a regular and robust daily rhythm. The circadian system optimizes the ability to sleep during the nighttime and the typical alert waking period from the morning through the evening hours. Melatonin and other melatonin agonists facilitate bedtime sleep onset by reducing the evening circadian arousal, thereby leaving the accumulated homeostatic sleepiness

drive unopposed. Accordingly, melatonin agonists would be expected to enhance sleep onset, as well as stabilize and possibly shift the timing of the circadian system, depending on the timing of the dose. Circadian timing, including the pronounced influence on the timing of sleep, is entrained primarily through light exposure from the photoperiod. The mechanism involves a nonvisual photochemical reaction in retinal ganglion cells with a compound called melanopsin. Light exposure information is transmitted through the relatively short retinohypothalamic tract to the suprachiasmatic nucleus, where the light/dark information is integrated to coordinate the timing of the circadian clock. Note that artificial light, particularly the blue end of the visual spectrum, can alter the rhythm therapeutically (eg, evening bright light exposure to purposely delay the cycle for people with abnormally advanced circadian cycles experiencing early morning awakening) or, much more commonly, can cause an inadvertent delay in the circadian system with later evening sleepiness and bedtime in association with exposure to closely held electronic screens (eg, smartphones, tablets, and laptops).

**Histamine 1 receptor antagonism.** Currently, the only selective  $\text{H}_1$  receptor antagonist approved by the FDA for treatment of insomnia is ultra-low-dose doxepin. The specific FDA-approved indication is for the management of sleep maintenance insomnia. Compared with other histaminergic compounds, ultra-low-dose doxepin is unusual for its very high specificity and selectivity for  $\text{H}_1$  receptor antagonist activity. Accordingly, the key pharmacodynamic action is antihistamine-promoted sedation. The available doses are as high as 150 mg/d, and the prescribing guidelines for treating depression are as high as



**FIGURE 8-6** The suprachiasmatic nucleus (SCN) as modulator of sleep and wakefulness. Modulation of sleep and wakefulness is a product of the interaction between several systems in the central nervous system. *A*, The SCN generates the alerting signals and is responsible for promoting wakefulness during the day. Throughout the daytime, melatonin levels are low, but gradually rise in the evening as a response to darkness. *B*, As bedtime ensues, melatonin levels continue to rise, peaking during the typical nighttime sleep hours and declining by the end of the night. The release of melatonin inhibits the wake signals generated in the SCN. As melatonin release diminishes later during the night, the wake-promoting signal from the SCN predominates and assumes control of the sleep-wake process as the night further progresses toward morning. Sunlight stimulates the SCN, maintaining arousal, while the pineal gland's release of melatonin is suppressed, supporting wakefulness.

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300 mg/d; however, the low-dose formulations approved for insomnia are just 3 mg and 6 mg before bedtime. Adverse events reported include somnolence, sedation, nausea, and upper respiratory tract infection. Ultra-low-dose doxepin should not be prescribed for patients with untreated narrow-angle glaucoma or severe urinary retention or for people also taking monoamine oxidase inhibitors. As with other tricyclic antidepressants, caution should be exercised with use in patients with cardiac disease given the risk for QT-interval prolongation, although with ultra-low-dose doxepin, this is unlikely. With no abuse poten-

tial, ultra-low-dose doxepin is considered a nonscheduled medication and is Pregnancy Category C.

**Hypocretin/orexin receptor antagonism.** Suvorexant is a novel hypnotic and is the only insomnia medication currently approved by the FDA that works specifically by blocking the wake-promoting effects of orexin/hypocretin. The medication is clinically indicated for insomnia characterized by sleep onset and/or maintenance.<sup>37,38</sup> Suvorexant is a hypocretin/orexin receptor antagonist that promotes sleep by blocking the arousal promoted by the hypocretin/orexin system, which, during the daytime and evening hours,



# KEY POINTS

- Several sedating antidepressant, antipsychotic, antiepileptic, antihypertensive, and other sedating psychotropic medications are occasionally prescribed by neurologists to specifically treat insomnia symptoms.
- All the available over-the-counter sleep aids contain antihistamines, with most containing diphenhydramine or doxylamine, which are first-generation antihistamines with anticholinergic and sedative properties.

helps to stabilize wakefulness. In contrast to other hypnotics, suvorexant blocks the binding of the neuropeptides (orexin-A and orexin-B). Suvorexant is labeled by the FDA as a Schedule IV controlled substance and confers a slight risk of abuse.<sup>39</sup> This drug is contraindicated in patients with narcolepsy and is a Pregnancy Category C drug. Suvorexant causes significant somnolence in 7% to 11% of patients, and clinically meaningful sedation can occur at higher doses.<sup>39</sup> Current recommendations advocate for a starting dose of 10 mg before bedtime and proceeding with either 15 mg or 20 mg before bedtime, if needed. The maximal FDA-labeled dosage is 20 mg/d, although, in clinical trial development, substantially higher doses of 30 mg/d to 100 mg/d were also used with more carryover sedation and some unfavorable increases in measured reaction time. Suvorexant should be used with caution in patients who are obese and in people taking CYP3A4 inhibitors.<sup>40</sup> One concern with the hypocretin/orexin antagonist approach to treating insomnia is the theoretical possibility of the intrusion of rapid eye movement (REM) phenomena into wakefulness. These might include sleep paralysis, hypnagogic/hypnopompic hallucinations, and symptoms similar to cataplexy. Suvorexant is contraindicated in patients with narcolepsy.

**General considerations when using hypnotic agents.** While the FDA-approved insomnia medications have indications for chronic insomnia, therapy should be weighed carefully given the patient phenotype, underlying comorbidities, and unique side effect profiles and warnings. The FDA has required certain warnings for all the insomnia medications. One warning relates to rare severe anaphylactic and anaphylactoid reactions. The other

broad warning targets possible abnormal thinking and behavior following hypnotic doses, and it notes the potential for complex behaviors associated with amnesia, examples of which include driving, preparing and eating foods, talking on the telephone, and engaging in sexual behaviors when not fully awake. Patients are advised to discontinue the medication if these symptoms occur. Other general warnings relate to the potential for next-day drowsiness or impairment and ensuring that patients have sufficient time in bed following a medication dose.

**Off-label prescription insomnia pharmacotherapy.** Several sedating antidepressant, antipsychotic, antiepileptic, antihypertensive, and other sedating psychotropic medications are occasionally prescribed to treat insomnia symptoms. While sometimes helpful, insufficient evidence of the safety and efficacy of these medications exists to support their use to treat these disorders, particularly in neurology patients who are often vulnerable to treatment-related adverse effects, particularly with agents that confer respiratory depression in the setting of neuromuscular disease, amnesia, memory difficulty, and daytime sedation. Prescribers should be mindful of the risk-to-benefit ratio of these agents for insomnia. Specific examples include the sedating antidepressants, such as trazodone, amitriptyline, mirtazapine, and conventional clinical doses of doxepin, which often have been prescribed in this manner. Quetiapine has been prescribed for insomnia; however, it can increase the risk of bleeding when taken concomitantly with warfarin<sup>41</sup> and may place those with concomitant cardiovascular disease at higher risk of mortality because of QT-interval prolongation.<sup>42</sup>

**Over-the-counter sleep aids.** All the available over-the-counter sleep aids contain antihistamines, with most

containing diphenhydramine or doxylamine, which are first-generation antihistamines with anticholinergic and sedative properties. The over-the-counter sleep aids are marketed as single compounds or are provided as a combination therapy with analgesics (ibuprofen or acetaminophen), formulated as evening preparations. While the antihistamine sedating effect is the desired activity, these agents may exert adverse and sometimes serious side effects. Most concerning are the anticholinergic effects, which may contribute to delirium, confusion, dry mouth, constipation, and urinary retention. These agents should be used with greater caution in older adults and patients receiving other anticholinergics. Another concern is that these drugs have relatively long durations of action that may lead to next-morning drowsiness following nighttime dosing. Tolerance may develop, with chronic usage leading to inappropriate dose escalation.<sup>43</sup>

**Unregulated compounds.** These substances are marketed as dietary supplement sleep aids and often are considered in the realm of complementary and alternative medicine. These unregulated sleep aids are generally promoted as single or multiple compounds containing plant-derived ingredients such as chamomile, passionflower, valerian, hops, and kava kava.

Tart cherry juice was found to be associated with anecdotal subjective reports of sleep enhancement in people with insomnia.<sup>44</sup> While the effect sizes were moderate and in some cases negligible, the data suggest that a tart cherry juice blend has modest efficacy in the management of insomnia in older adults with insomnia.<sup>44</sup>

At present, with rare exceptions, few convincing data exist regarding efficacy of these dietary supplements. Patients should be warned, however, that while these unregulated dietary

compounds may be marketed as “natural,” they are not necessarily safe. One notable example is kava kava, which may be associated with hepatic toxicity.<sup>45,46</sup> Because the evidence is not complete, risk-benefit assessments are not reliable, and much knowledge is still lacking.

Melatonin is a unique member of the dietary supplement sleep aid category in the United States, since it is a compound with an established role in sleep physiology and demonstrated efficacy in treating circadian rhythm sleep-wake disorders. It is a neurohormone produced by the pineal gland that can reset sleep onset by synchronization of the internal circadian clock. With advanced age, less melatonin is produced, and is often an underlying cause contributing to advanced sleep-wake phase disorder in older age. Circulating melatonin levels are significantly lower in many elderly patients with insomnia compared to controls, and melatonin onset and peak times are delayed. Melatonin replacement may be beneficial for elderly patients experiencing insomnia. Currently, however, more data are needed to improve our understanding of the appropriate dosage, pharmacologic properties, and indications. Melatonin is not FDA approved, formulations vary, and efficacy and safety data are still needed.

In the European Union, a prolonged-release melatonin formulation is available only by prescription. Prolonged-release melatonin is approved in the European Union for the treatment of primary insomnia characterized by poor sleep quality in patients aged 55 years and older.<sup>47</sup>

### **Developing an Insomnia Treatment Plan**

The evaluation of insomnia should foster a patient-specific customized plan for management that considers

#### **KEY POINT**

■ Melatonin is a unique member of the dietary supplement sleep aid category in the United States, since it is a compound with an established role in sleep physiology and demonstrated efficacy in treating circadian rhythm sleep-wake disorders.

**KEY POINTS**

- The evaluation of insomnia should foster a patient-specific customized plan for management that considers the unique insomnia phenotype, chief complaint specific to the timing and chronicity of the insomnia, underlying comorbidities, sleep-wake pattern symptoms, lifestyle pattern, social habits and routines, previously tried hypnotic therapy (specific agents, dose, duration, and development of adverse effects), and any prior cognitive-behavioral therapy for insomnia.
- The cornerstone of insomnia management for all patients must include education regarding proper sleep hygiene and individualized recommendations about proper sleep-enhancing behaviors.

the unique insomnia phenotype, chief complaint specific to the timing and chronicity of the insomnia, underlying comorbidities, sleep-wake pattern symptoms, lifestyle pattern, social habits and routines, previously tried hypnotic therapy (specific agents, dose, duration, and development of adverse effects), and any prior CBT-I.<sup>3</sup> Patients should be asked to share their specific expectations and treatment goals. Over time, clinicians should monitor symptoms regularly with patients to assess the effects of the therapeutic strategies implemented.

The cornerstone of insomnia management for all patients must include education regarding proper sleep hygiene and individualized recommendations about proper sleep-enhancing behaviors. Strategies reviewed by CBT-I specialists should be assimilated into the management plan and should occur in harmony and synchronously with any pharmacotherapy intervention.

FDA-approved hypnotics may be appropriate for initial use in treating patients with insomnia, especially because they are generally better studied in populations where treatment-emergent adverse effects are more

frequent. Prescribers should pay close attention to the pharmacodynamic and pharmacokinetic profiles and undertake therapy to address their patients' symptoms after carefully querying patients about circadian patterns, the nature of the underlying sleep disturbances, and potential impact on health-related quality of life. Careful attention to sleep-wake circadian patterns is especially important as one considers implementation of strategic light exposure in resynchronizing the sleep-wake pattern.

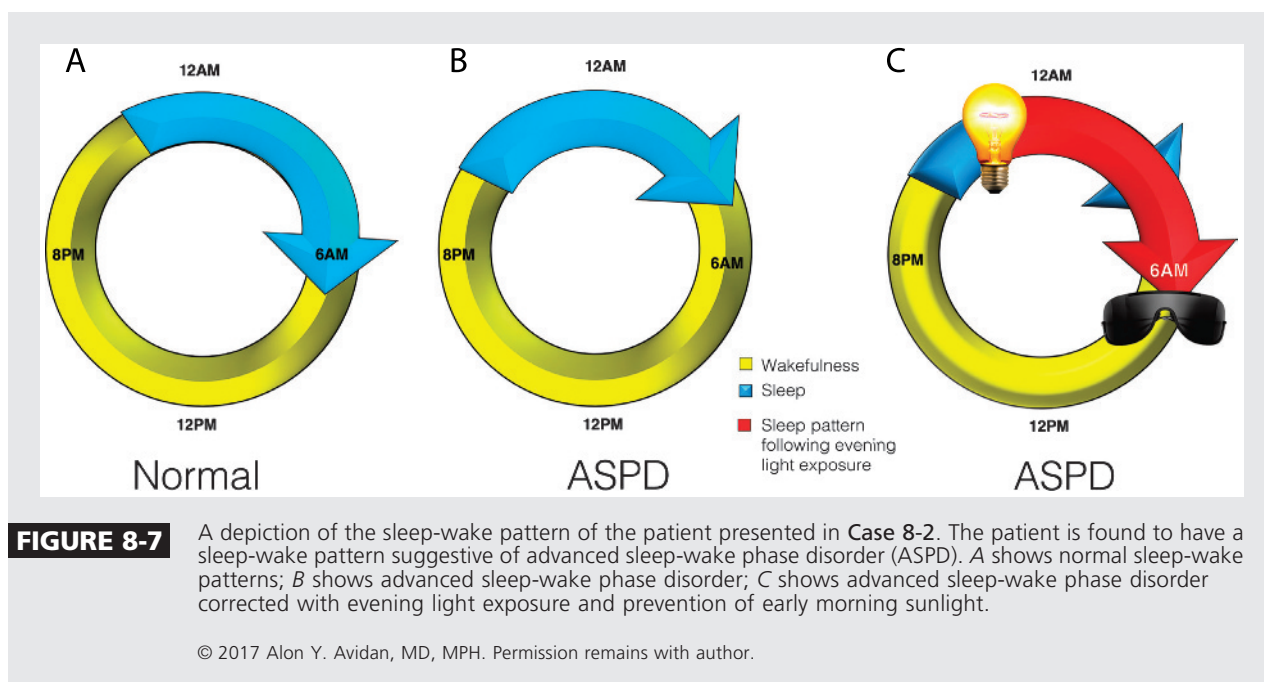
Advanced sleep-wake phase disorder is sometimes encountered among older patients and may be related to depressed melatonin production (**Case 8-2**).

Compared to the normal circadian rhythm demonstrated in **Figure 8-7A**, patients with a phase-advanced cycle generally get sleepy early in the evening and wake up early in the morning, when they are then usually unable to reinitiate sleep (**Figure 8-7B**). Although the older adult may get sleepier in the evening, he or she often still tries to remain awake until a more socially acceptable time (ie, 10:00 PM to 11:00 PM). Then, when the patient awakens early and is

**Case 8-2**

An 82-year-old man with mild Alzheimer disease presented for evaluation of early morning awakening and the inability to return to sleep. He often became very tired around 6:00 PM and fell asleep around 8:00 PM. He had no difficulty falling asleep. However, when he woke up at around 2:30 AM to 3:00 AM, he was unable to reinitiate sleep. He then stayed awake in bed until about 7:00 AM, when he finally got out of bed and began his day. He denied any symptoms of depression other than his sleep problems.

**Comment.** This man has insomnia in the setting of advanced sleep-wake phase disorder. The sleep-wake cycle is controlled by the circadian modulator located in the suprachiasmatic nucleus of the anterior hypothalamus. *Zeitgebers*, external cues (predominantly the photoperiod), synchronize the circadian cycle. Disturbances in circadian rhythms are due to a mismatch between the environmental cues and the endogenous circadian rhythms. The hypersomnolence seen in an older person may be due in part to a disintegration of the normal circadian rhythm.



unable to fall back to sleep, time in bed has not been long enough for a sufficient sleep amount, resulting in a state of sleep deprivation. Advanced sleep-wake phase disorder can be treated with bright light therapy during the later afternoon/early evening timeframe, as light is one of the strongest cues for synchronizing circadian rhythms and can delay the sleep cycle when given at this time. Early morning bright light exposure should be avoided since it can further advance the sleep cycle at that time, and the use of sunglasses following dawn may be helpful. One strategy for bright light therapy for this disorder involves exposure to at least 5000 lux for 2 hours in the evening (eg, 7:00 PM to 9:00 PM) at about 1 meter eye level (Figure 8-7C).<sup>48</sup>

## CONCLUSION

Chronic insomnia in neurology practice represents a unique opportunity for clinicians to help improve the quality of life across patients with

comorbid neurologic conditions. All patients should be screened to help uncover poor sleep behaviors since insomnia may exacerbate health problems, undermine the quality of sleep, limit the ability to remain awake, and worsen daytime function. As with the approach to other neurologic presentations, the neurologist should conduct a careful sleep history. Insomnia should be considered in every patient, especially those who present with refractory pain, headaches, seizures, and impaired cognition. The treatment approach should incorporate evidence-based therapies, including CBT-I and appropriately selected pharmacotherapies based on the timing of sleep difficulty during the sleep cycle. Even neurologists without specific training in sleep medicine should take opportunities to address the effects of insomnia by integrating proper pharmacologic and behavioral treatment approaches, especially given the pervasive nature of sleep difficulties among neurologic patients.



## USEFUL WEBSITES

### 2017 Insomnia Clinical Guideline from the American Academy of Sleep Medicine

*aasmnet.org/Resources/clinicalguidelines/040515.pdf*

### Insomnia Practice Parameters from the American Academy of Sleep Medicine

*aasmnet.org/practiceparameters.aspx?cid=109*

### Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update. An American Academy of Sleep Medicine Report

*aasmnet.org/Resources/PracticeParameters/PP\_BTInsomnia\_Update.pdf*

### Quality Measures for the Care of Patients with Insomnia from the American Academy of Sleep Medicine

*aasmnet.org/Resources/QualityMeasures/QualityMeasuresfortheCareofPatientswithInsomnia.pdf*

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# Sleep-Disordered Breathing

Nancy R. Foldvary-Schaefer, DO, MS; Tina E. Waters, MD

## ABSTRACT

**Purpose of Review:** Sleep-disordered breathing encompasses a broad spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea, as well as sleep-related hypoventilation and hypoxemia. Diagnostic criteria have been updated in the *International Classification of Sleep Disorders, Third Edition* and the *American Academy of Sleep Medicine Manual for Scoring Sleep and Associated Events*. Neurologic providers should have basic knowledge and skills to identify at-risk patients, as these disorders are associated with substantial morbidity, the treatment of which is largely reversible.

**Recent Findings:** OSA is the most common form of sleep-disordered breathing and is highly prevalent and grossly underdiagnosed. Recent studies suggest that prevalence rates in patients with neurologic disorders including epilepsy and stroke exceed general population estimates. The physiologic changes that occur in OSA are vast and involve complex mechanisms that play a role in the pathogenesis of cardiovascular and metabolic disorders and, although largely unproven, likely impact brain health and disease progression in neurologic patients. A tailored sleep history and examination as well as validated screening instruments are effective in identifying patients with sleep-disordered breathing, although sleep testing is necessary for diagnostic confirmation. While continuous positive airway pressure therapy and other forms of noninvasive positive pressure ventilation remain gold standard treatments, newer therapies, including mandibular advancement, oral appliance devices, and hypoglossal nerve stimulation, have become available. Emerging evidence of the beneficial effects of treatment of sleep-disordered breathing on neurologic outcomes underscores the importance of sleep education and awareness for neurologic providers.

**Summary:** Sleep-disordered breathing is highly prevalent and grossly underrecognized. The adverse medical and psychosocial consequences of OSA and other sleep-related breathing disorders are considerable. The impact of sleep therapies on highly prevalent neurologic disorders associated with substantial morbidity and health care costs is becoming increasingly recognized.

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## INTRODUCTION

Sleep-disordered breathing is characterized by abnormalities of respiration during sleep that include obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder.<sup>1</sup> Of these, OSA is the most common in all ages. This

article reviews the epidemiology, pathophysiology, clinical presentation, diagnostic criteria, and treatment of this group of disorders, with an emphasis on OSA in adults.

## SLEEP APNEA SYNDROMES

Sleep apnea syndromes are classified as obstructive or central based



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**KEY POINT**

■ The severity of obstructive sleep apnea is determined by the apnea-hypopnea index during polysomnography, with mild obstructive sleep apnea having an apnea-hypopnea index of 5 to 14 per hour, moderate obstructive sleep apnea having an apnea-hypopnea index of 15 to 29 per hour, and severe obstructive sleep apnea having an apnea-hypopnea index of 30 or more per hour.

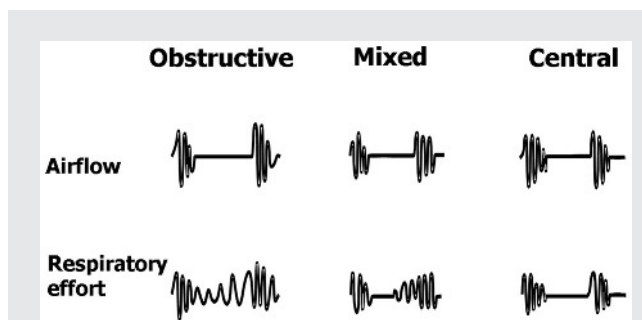
on polysomnographic event scoring, according to the American Academy of Sleep Medicine (AASM).<sup>2</sup> Respiratory events are classified as apneas and hypopneas; apneas are further subdivided into obstructive, central, or mixed (**Figure 9-1**). Obstructive apneas are episodes of complete upper airway collapse, defined as a greater than 90% drop in the airflow/thermal sensor in the presence of continued respiratory effort lasting at least 10 seconds. Hypopnea is defined as a 30% or more drop in the nasal pressure signal lasting for at least 10 seconds, associated with a 3% or more oxygen desaturation or an arousal (AASM-recommended definition) or 4% or more oxygen desaturation (AASM-acceptable definition, Centers for Medicare and Medicaid Services definition).<sup>2</sup> Hypopneas are generally considered to be obstructive events representing partial upper airway collapse. In contrast, central apnea is defined as a greater than 90% drop in the airflow/thermal sensor accompanied by absent respiratory effort that lasts for at least 10 seconds. Mixed apnea is characterized by a greater than 90% drop in the airflow/thermal sensor lasting at least 10 seconds and

associated with initial absence of respiratory effort that resumes despite continued absent airflow.

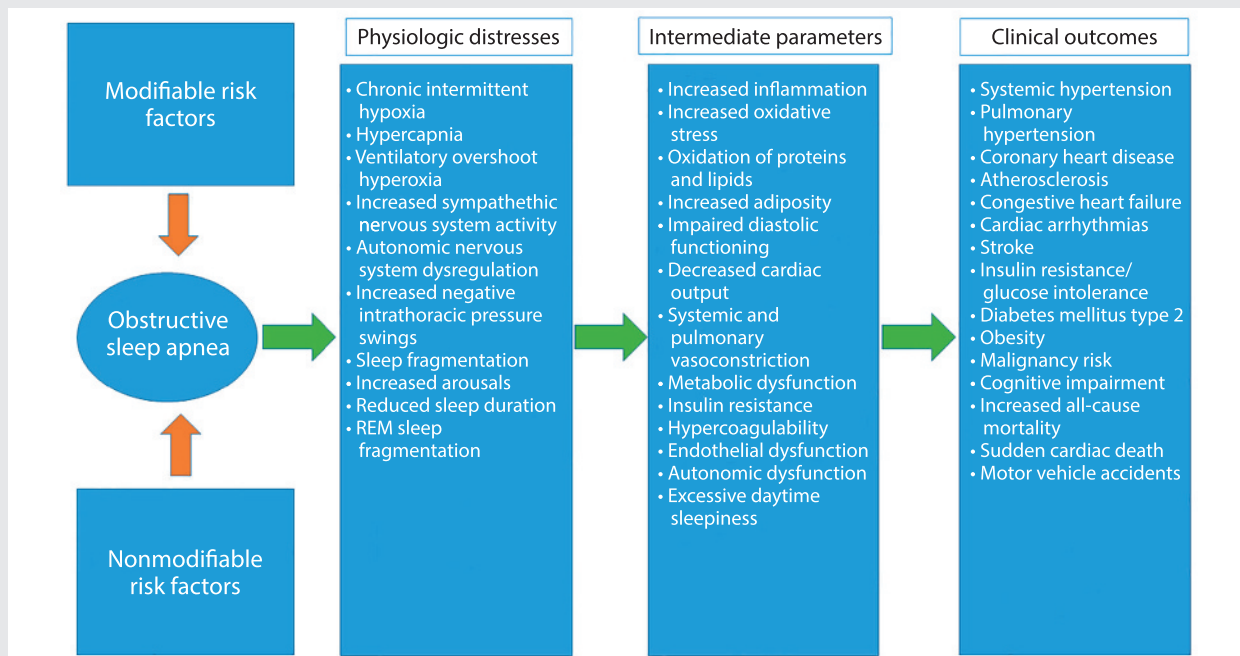
The severity of sleep apnea is defined by the apnea-hypopnea index (AHI), a ratio of the sum of all respiratory events to the total hours of sleep on polysomnography or home sleep apnea testing. By convention, an AHI of 5 to 14 per hour defines mild sleep apnea, an AHI of 15 to 29 per hour is moderate sleep apnea, and an AHI of 30 or more per hour is severe sleep apnea, although the presence of significant oxygen desaturation or ECG abnormalities may imply more significant pathology than the AHI alone (**Figure 9-2**).<sup>3</sup> The respiratory disturbance index is an alternative measurement of sleep apnea severity. Like the AHI, the respiratory disturbance index measures sleep apnea severity but includes respiratory effort-related arousals, which are episodes of increasing respiratory effort lasting for at least 10 seconds that lead to an arousal but do not fulfill the criteria for a hypopnea or apnea due to less oxygen desaturation.

**Obstructive Sleep Apnea**

OSA is characterized by repetitive episodes of partial (hypopnea) or complete (apnea) obstruction of the upper airway during sleep.<sup>1</sup> Diagnostic criteria are shown in **Table 9-1** and include either an obstructive AHI of at least 15 per hour or at least 5 per hour when accompanied by at least one symptom of excessive daytime sleepiness; nonrestorative sleep; fatigue; insomnia; waking with breath holding; gasping or choking; observer reports of loud snoring, breathing interruptions, or both; or a comorbid condition including hypertension, mood disorder, cognitive dysfunction, coronary artery disease, or type 2 diabetes mellitus.<sup>1</sup> When OSA, defined

**FIGURE 9-1**

Types of apnea. Obstructive apnea is characterized by cessation of airflow with persistent respiratory effort. Mixed apnea is characterized by initial cessation of airflow and respiratory effort followed by resumption of respiratory effort while airflow cessation persists. Central apnea is characterized by a cessation in airflow and respiratory effort for the duration of the event.



**FIGURE 9-2** Consequences of obstructive sleep apnea because of physiologic stressors, intermediate parameters, and clinical outcomes.

REM = rapid eye movement.

Modified with permission from May AM, Mehra R, Semin Respir Crit Care Med.<sup>3</sup> © 2014 Thieme Medical Publishers, Inc. [thieme-connect.com/DOI/DOI?10.1055/s-0034-1390023](http://thieme-connect.com/DOI/DOI?10.1055/s-0034-1390023).

**TABLE 9-1** Diagnostic Criteria for Obstructive Sleep Apnea<sup>a</sup>

**Criteria 1 and 2 or 3 must be met for a diagnosis of obstructive sleep apnea**

1. One or more of the following must be present:
  - A. Excessive sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
  - B. Waking with breath holding, gasping, or choking
  - C. Observer reports of snoring, breathing interruptions, or both, during sleep
  - D. Diagnosis of hypertension, coronary artery disease, stroke, heart failure, atrial fibrillation, type 2 diabetes mellitus, mood disorder, or cognitive impairment

AND

2. Polysomnography or home sleep apnea test demonstrates five or more predominantly obstructive respiratory events per hour of sleep (polysomnography) or per hour of monitoring (home sleep apnea test)

OR

3. Polysomnography or home sleep apnea test demonstrates 15 or more predominantly obstructive respiratory events per hour of sleep (polysomnography) or per hour of monitoring (home sleep apnea test)

<sup>a</sup> Data from the American Academy of Sleep Medicine.<sup>1</sup>



**KEY POINT**

- Approximately 15% of adults have moderate to severe obstructive sleep apnea.

by polysomnography, is associated with daytime symptoms such as excessive daytime sleepiness, OSA syndrome is present.

**Pathophysiology.** Repetitive obstructive respiratory events occur during sleep. These events can result in reductions in oxyhemoglobin saturation and may be terminated by arousal, leading to sleep fragmentation. The oxygen saturation level usually returns to baseline following resumption of normal breathing, but may remain low if the respiratory events are frequent or prolonged or occur in the presence of underlying pulmonary pathology. Respiratory events occur more frequently in sleep stages N1 (non-rapid eye movement [non-REM] 1), N2 (non-REM 2), and REM and are usually longer and associated with more severe desaturation while in REM sleep and in the supine position. By contrast, sleep stage N3 (non-REM 3) is protective against OSA, with less frequent and severe desaturations. The upper airway in OSA is abnormally collapsible, with reduced genioglossus and upper airway dilator muscle activity, or is partially occluded because of upper airway or craniofacial pathology. Individuals with OSA have a higher critical closing pressure, which is greater than atmospheric pressure, whereas healthy individuals have a critical closing pressure that is subatmospheric.<sup>4</sup>

**Epidemiology.** OSA prevalence estimates, defined as an AHI of 5 or more per hour on polysomnography, are 24% for men and 9% for women, based on the Sleep Heart Health Study published more than 2 decades ago, when obesity rates were much lower than today.<sup>5</sup> More recent data from the Wisconsin Sleep Study Cohort indicate that 10% of men and 3% of women 30 to 49 years of age and 17% of men and 9% of women 50 to 70 years of age have moderate to severe OSA.<sup>6</sup> In

patient populations with certain medical comorbidities, the prevalence of OSA exceeds that of the general population (Table 9-2).<sup>7,8</sup>

Epidemiologic investigations of OSA are based on variable sample

**TABLE 9-2 Clinical Characteristics Suggestive of Obstructive Sleep Apnea**

- ▶ **Standard<sup>b</sup>**
  - Obesity
  - Heart failure
  - Preoperative upper airway surgery
- ▶ **Guideline<sup>c</sup>**
  - Coronary artery disease
  - Tachyarrhythmia/bradyarrhythmia
  - Atrial fibrillation
- ▶ **Option<sup>d</sup>**
  - Stroke
  - Transient ischemic attack
- ▶ **Consensus<sup>e</sup>**
  - Hypertension/refractory hypertension
  - Type 2 diabetes mellitus
  - Pulmonary hypertension
  - Preoperative bariatric surgery
  - High-risk driving populations

<sup>a</sup> Data from Epstein LJ, et al, *J Clin Sleep Med*.<sup>7</sup> [aasmnet.org/Resources/clinicalguidelines/OSA\\_Adults.pdf](http://aasmnet.org/Resources/clinicalguidelines/OSA_Adults.pdf).

<sup>b</sup> Standard reflects a high degree of clinical certainty based on Level 1 evidence or overwhelming Level 2 evidence.

<sup>c</sup> Guideline reflects a moderate degree of clinical certainty, based on Level 2 evidence or a consensus of Level 3 evidence.

<sup>d</sup> Option reflects uncertain clinical use, implying insufficient, inconclusive, or conflicting evidence or conflicting expert opinion.

<sup>e</sup> Consensus recommendations address areas of clinical practice where available empirical data are limited or inconclusive.

selection (clinic-based versus random population), sleep study assessment, and event scoring criteria, limiting direct comparisons across studies. Despite these variations, comparison of several studies yields similar preva-

lence rates for moderate to severe OSA across a range of ethnic groups (Table 9-3). Compared to the white population, the prevalence of OSA is higher in the Hispanic population and as high or higher in the African

**TABLE 9-3 Population-Based Obstructive Sleep Apnea Prevalence**

Study and Age of Participants	Number of Subjects	Apnea-Hypopnea Index $\geq 5$	Apnea-Hypopnea Index $\geq 15$	Obstructive Sleep Apnea Syndrome
Pennsylvania, United States, 1998, <sup>9</sup> 2001 <sup>10</sup>				
20–100 years of age				
Men	741	17%	7%	3.3%
Women	1000	5%	2%	1.2%
Spain, 2001 <sup>11</sup>				
30–70 years of age				
Men	325	26%	14%	3.4%
Women	235	28%	7%	3%
Hong Kong, China, 2001, <sup>12</sup> 2004 <sup>13</sup>				
30–60 years of age				
Men	153	8.8%	5.3%	4.1%
Women	106	3.7%	1.2%	2.1%
Cleveland, Ohio, United States, 2002 <sup>5</sup>				
40–98 years of age				
Men	2648	58%	25%	NA
Women	2967	37%	11%	NA
Korea, 2004 <sup>14</sup>				
40–69 years of age				
Men	309	27%	10.1%	4.5%
Women	148	16%	4.7%	3.2%
India, 2006 <sup>15</sup>				
30–60 years of age				
Men	88	19.7%	NA	4.9%
Women	63	7.4%	NA	2.1%
Wisconsin, United States, 2013 <sup>6</sup>				
30–49 years of age				
Men	55%	26.6%	10%	11.7%
Women	45%	8.7%	3%	2.9%
50–70 years of age				
Men	55%	43.2%	17%	17.6%
Women	45%	27.8%	9%	7.5%

NA = not applicable.

**KEY POINTS**

- Women with obstructive sleep apnea have lower apnea-hypopnea indexes when matched to men for body weight, have less supine position dependency, and experience more rapid eye movement dependency of events. Women may also experience less snoring and witnessed apnea, but more insomnia and fatigue, and have lower survival rates compared to men with similar apnea-hypopnea indexes.
- A 10% increase in weight is associated with a 30% increase in the apnea-hypopnea index.

American population. Variations in upper airway soft tissue structure, craniofacial anatomy, and obesity between groups likely contribute to the variations in OSA frequency across populations.

Several studies found OSA to be highly prevalent in elderly populations. The Osteoporotic Fractures in Men (MrOs) Sleep Study found moderate OSA in 30% of men older than 80 years, 3 times higher than middle-aged individuals.<sup>16</sup> If aging is a risk factor for OSA, the prevalence would be expected to continue rising over time; however, studies suggest that most of the age-related prevalence increase occurs before age 65 years, the reasons for which are still unclear.<sup>8,16</sup> The 5-year incidence rate for moderate OSA is 11.1% for men and 4.9% for women based on data from the Sleep Heart Health Study.<sup>17</sup> The trend is for the overall AHI to increase over time regardless of gender, body mass index (BMI), age, and habitual snoring status.<sup>8</sup>

Several differences in OSA presentation are observed between genders. While OSA is less common in premenopausal women than in men, the risk increases after menopause such that older women and men are nearly comparably affected.<sup>18</sup> The prevalence is lower in postmenopausal women using hormone replacement therapy, suggesting a protective role of progesterone and estrogen on upper airway dilator muscle activity.<sup>19</sup> Women with OSA have lower AHIs when matched to men for body weight, which is believed to be due to less upper airway collapsibility and structural differences or fat deposition in the upper airway. Women also have less supine position dependency and more REM dependency of respiratory events.<sup>20</sup> Finally, women report less snoring and witnessed apnea and more insomnia, excessive daytime sleepiness, and fatigue<sup>21,22</sup> and have lower survival rates compared

to men with similar AHIs,<sup>23</sup> perhaps because of their nonclassic presentation, resulting in diagnostic delay.

Risk factors for OSA are both modifiable and nonmodifiable. Modifiable risk factors include obesity, sedative medications, alcohol, tobacco use, endocrine disorders (eg, hypothyroidism, polycystic ovary syndrome, acromegaly), and nasal obstruction/congestion. In addition to gender, age, ethnicity, and menopausal status, nonmodifiable factors include genetic predisposition, craniofacial anomalies, and congenital syndromes, including Treacher Collins and Pierre Robin syndromes.

Obesity, defined as a BMI of 30 kg/m<sup>2</sup> or more, is a firmly established risk factor for OSA. However, not all patients who are obese develop OSA, and not all people with OSA are obese. Obesity alters the geometry and function of the upper airway, leading to increased collapsibility, especially in the lateral aspects of the pharynx. The odds of incident OSA increase sixfold with a 10% weight gain, resulting in a 30% increase in AHI.<sup>24</sup> The association between BMI and OSA is present, but is weaker in children and the elderly.

Neck circumference, a surrogate for obesity, is independently associated with OSA. Greater neck fat distribution contributes to mass loading on the upper airway. Individuals with OSA have a larger neck circumference compared to nonapneic snorers. A neck circumference of greater than 40 cm (15.7 inches) has been shown to be predictive of OSA, with 61% sensitivity and 93% specificity, regardless of gender.<sup>25</sup>

The Cleveland Family Study found a familial aggregation of OSA. Families with an index case of sleep apnea had a higher prevalence than those without (21% versus 9%), and the risk increased with additional affected members.<sup>26</sup>

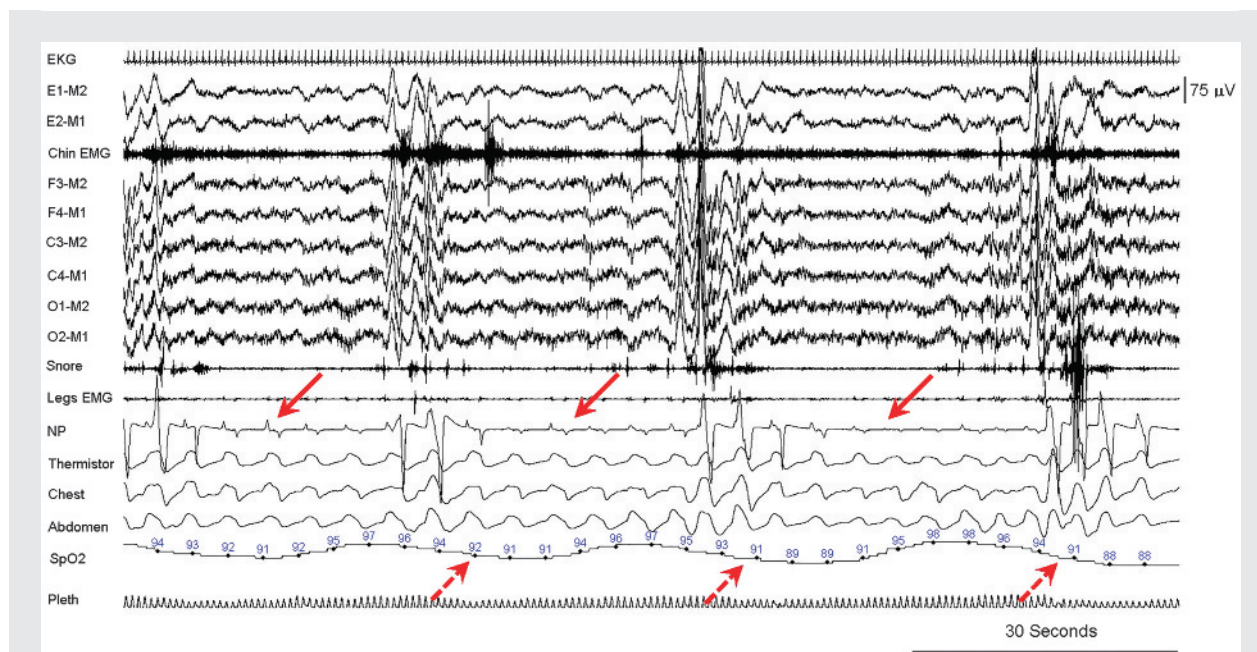
Certain craniofacial features and congenital syndromes affecting craniofacial and upper airway anatomy predispose patients to OSA. Individuals with maxillary hypoplasia and micrognathia are particularly susceptible. Patients with Down syndrome are particularly predisposed to OSA, with prevalence estimates of 24% to 57%, as a result of unique upper airway anatomic features, obesity, hypothyroidism, gastroesophageal reflux disease, and generalized hypotonia.<sup>27</sup>

**Physiologic consequences of obstructive sleep apnea.** The physiologic changes that occur in OSA are vast and involve complex mechanisms, which increase the risk of cardiovascular and metabolic adverse outcomes (Figure 9-3).<sup>3</sup> Increased respiratory effort against a closed airway leads to an increase in negative intrathoracic pressure, which affects left-sided filling mechanics and can lead to impaired cardiac functioning, vasoconstriction,

and atrial and aortic enlargement. The hypoxemia, hypercapnia, and arousal response associated with recurrent obstructive events results in sympathetic nervous system overdrive, which can lead to changes in autonomic regulation of blood pressure and loss of the normal circadian rhythm of blood pressure dipping during sleep. OSA has proinflammatory effects, resulting in upregulation of inflammatory mediators including interleukin-6, soluble interleukin-6 receptor, interleukin-8, tumor necrosis factor, C-reactive protein, and nuclear factor kappa light chain-enhancer of activated B cells. Enhanced thrombotic potential via stimulation of plasminogen activator inhibitor-1, fibrinogen, P selectin, and vascular endothelial growth factor is observed. Accumulation of reactive oxygen species in the setting of recurrent hypoxia is associated with endothelial dysfunction via increased oxidative stress and oxidation of serum

#### KEY POINT

■ Vast physiologic changes in obstructive sleep apnea involve complex mechanisms that increase the risk of cardiovascular and metabolic adverse outcomes via sympathetic nervous system overdrive, proinflammatory effects, enhanced thrombotic potential, and oxidative stress.



**FIGURE 9-3** Obstructive hypopnea. A 2-minute epoch during stage N2 sleep showing recurrent obstructive hypopneas (solid arrows). Note the persistence of airflow and respiratory effort in the presence of reduced nasal pressure (NP) signal. Events are terminated by arousal and associated with oxygen desaturations (dashed arrows).



**KEY POINT**

■ Although self-reported instruments are available to assist in identifying high-probability obstructive sleep apnea, not everyone has a bed partner, and affected individuals may be unaware of snoring/apneic events during sleep, and patients often underestimate the degree of their daytime sleepiness and fatigue.

proteins and lipids, which facilitates the development of atherosclerotic changes. Sleep fragmentation and restriction reduces glucose tolerance, increases evening cortisol concentrations, and reduces insulin release, the combination of which can lead to insulin resistance and type 2 diabetes mellitus.

**Clinical evaluation.** A comprehensive sleep history allows for the identification of patients with a high probability of moderate to severe OSA, comorbid sleep disorders, and medical and psychiatric disorders that may impact treatment options and outcomes. Common symptoms of OSA are listed in Table 9-4.<sup>1</sup> It is important to note that not everyone has a bed partner, and affected individuals may be unaware of snoring and apneic events in sleep. Additionally, patients often underestimate the

degree of daytime sleepiness, particularly when long-standing or in the setting of chronic comorbidities that contribute to excessive daytime sleepiness and fatigue.

Several self-reported instruments are available to assist in the clinical determination of OSA. Largely validated in middle-aged population samples, their performance characteristics have not been established in patients with neurologic diseases or in the setting of other significant medical comorbidities. The most widely used screening questionnaire is the STOP questionnaire, which was later expanded to the STOP-BANG questionnaire (Table 9-5).<sup>28</sup> The presence of at least two symptoms on the four-item STOP questionnaire was found to have a moderately high sensitivity and negative predictive value. In comparison to the STOP, the STOP-BANG questionnaire, on which at least three items are predictive of OSA, the sensitivity for moderate OSA increased from 74.3% to 92.9%, and the negative predictive value increased from 76% to 90.2%.<sup>28</sup> Therefore, lower STOP-BANG scores (less than 3) can be used to help rule out OSA, while higher scores (5 to 8) can be used to help rule in OSA for patients requiring further objective confirmation with sleep studies when all clinical information and examination findings are considered.

The other most commonly used instrument for excessive daytime sleepiness is the Epworth Sleepiness Scale (Supplemental Digital Content Appendix, [links.lww.com/CONT/A222](http://links.lww.com/CONT/A222)). The Epworth Sleepiness Scale measures daytime sleep propensity by rating the chance of dozing in eight soporific situations (sitting and reading, watching television, sitting inactive in a public place, being a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit,

**TABLE 9-4** Common Presenting Symptoms of Obstructive Sleep Apnea

- **Daytime**
  - Excessive sleepiness that may include drowsy driving
  - Fatigue
  - Impaired memory/concentration
  - Irritability, depressed mood
  - Decreased libido
  - Morning headache
- **Nighttime**
  - Snoring
  - Gasping, choking, witnessed apnea by observer
  - Night awakenings, restless sleep
  - Nocturia
  - Night sweats
  - Dry mouth
  - Nocturnal gastroesophageal reflux



**TABLE 9-5 STOP-BANG Questionnaire<sup>a,b</sup>**

**1. Snoring**

Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

Yes/No

**2. Tired**

Do you often feel tired, fatigued, or sleepy during the daytime?

Yes/No

**3. Observed**

Has anyone observed you stop breathing during your sleep?

Yes/No

**4. Blood pressure**

Do you have or are you being treated for high blood pressure?

Yes/No

**5. BMI**

BMI more than 35 kg/m<sup>2</sup>?

Yes/No

**6. Age**

Age more than 50 years old?

Yes/No

**7. Neck circumference**

Neck circumference greater than 40 cm (15.75 inches)?

Yes/No

**8. Gender**

Gender male?

Yes/No

<sup>a</sup> Reprinted with permission from Chung F, et al, *Anesthesiology*.<sup>28</sup> © 2008 Wolters Kluwer Health, Inc. [anesthesiology.pubs.asahq.org/article.aspx?articleid=1932315#67929466](http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1932315#67929466).

<sup>b</sup> High risk of obstructive sleep apnea: answering yes to three or more items. Low risk of obstructive sleep apnea: answering yes to fewer than three items. BMI = body mass index.

range from never to a high chance of dozing, yielding total scores of 0 to 24. Scores of greater than 10 distinguish excessive daytime sleepiness from normal daytime sleepiness, with a sensitivity of 94% and a specificity of 100%.<sup>29</sup> The Sleep Heart Health Study identified a significant positive correlation between the Epworth Sleepiness Scale score and AHI independent of age, gender, ethnicity, BMI, and insufficient sleep time.<sup>30</sup> The Epworth Sleepiness Scale scores inconsistently correlate with the mean sleep latency on the multiple sleep latency test, suggesting that the two measures assess different aspects of excessive daytime sleepiness.<sup>31</sup>

The physical examination should be directed at assessing the probability of OSA and relevant comorbid conditions. Physical examination findings that may suggest the presence of OSA are listed in **Table 9-6**.<sup>1</sup> Pharyngeal and craniofacial morphology play an important role, as anatomic variants can result in a crowded oropharyngeal space or tongue displacement against the retropharyngeal region, leading to a predisposition to obstruction during sleep.

Different schemes have been devised to grade oropharyngeal anatomy. Using the Friedman tongue position classification (**Figure 9-4**), grade III (only the soft palate is visible) and grade IV (only the hard palate is visible) airways raise concern for significant oropharyngeal crowding. Patients with OSA more often have a Friedman grade III or IV than those without OSA (78% versus 46%).<sup>32</sup>

### Central Sleep Apnea

CSA, characterized by repetitive cessation of both airflow and ventilatory effort during sleep, is seen in a variety of settings, including periodic breathing in infancy, healthy adults at altitude, and

sitting and talking to someone, sitting quietly after lunch without alcohol, and sitting in a car while stopped for a few minutes in traffic). Responses

### KEY POINTS

- Central sleep apnea, characterized by repetitive cessation of both airflow and ventilatory effort during sleep, is seen in a variety of settings, including periodic breathing in infancy, healthy adults at altitude, and Cheyne-Stokes respiration in heart failure.
- Common risk factors for central sleep apnea include an age of 65 years or older, male gender, opioid use, comorbid heart failure, stroke, atrial fibrillation, and renal failure.

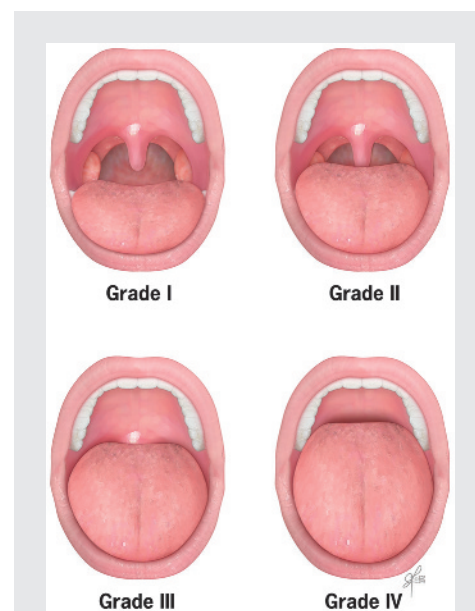
**TABLE 9-6** Physical Examination Findings Supportive of Obstructive Sleep Apnea

- ▶ Body mass index of more than 30 kg/m<sup>2</sup>
- ▶ Neck circumference of more than 43 cm (17 inches) in men and more than 40.6 cm (16 inches) in women
- ▶ Nasal obstruction (turbinate hypertrophy, septal deviation, polyps)
- ▶ Nasal valve incompetence
- ▶ Mandibular retrognathia, or micrognathia
- ▶ Macroglossia
- ▶ Scalloping along lateral tongue
- ▶ Small oral cavity (overlapping teeth)
- ▶ Low-hanging and elongated soft palate
- ▶ High-arched or narrow hard palate
- ▶ Large, elongated, or swollen uvula
- ▶ Overjet or malocclusions
- ▶ Tonsillar hypertrophy
- ▶ Lateral peritonsillar narrowing

Cheyne-Stokes respiration in heart failure. The *International Classification of Sleep Disorders, Third Edition (ICSD-3)* defines different types of CSA syndromes.<sup>1</sup> In general, the diagnostic criteria require at least one of the following symptoms: daytime sleepiness, difficulty initiating or maintaining sleep, frequent awakenings, nonrestorative sleep, snoring or witnessed apneas, or awakening short of breath. At least five central apneas or central hypopneas per hour of sleep are observed on polysomnography, and the total number of central events must be greater than 50% of the total number of all apneas and hypopneas.<sup>1</sup>

Common risk factors include age of more than 65 years, male gender, opioid use, and cardiovascular and medical comorbidities, such as heart failure, stroke, atrial fibrillation, and renal failure.

In most cases of CSA, the cyclic absence of effort is a paradoxical consequence of hypersensitive ventilatory chemoreflex responses that oppose changes in airflow, producing elevated loop gain and leading to overshoot/undershoot ventilatory oscillations.<sup>33</sup> Factors influencing loop gain include increased chemosensitivity (increased controller gain), reduced damping of blood gas levels (increased plant gain), and increased lung to chemoreceptor circulatory delay. Sleep-wake transitions and pharyngeal dilator muscle



**FIGURE 9-4** Tongue position. The Friedman classification is based on visualization of intraoral structures with the mouth open and tongue relaxed and not protruded (grade I: entire uvula and tonsils are visible; grade II: some of the uvula, but not the tonsils, is visible; grade III: only the soft palate is visible; grade IV: only the hard palate is visible).

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responses raise the controller gain, contributing to loop gain and ventilatory instability. Therapies for CSA affect loop gain by improving lung volume (positive airway pressure [PAP] therapy), reducing the alveolar-inspired  $P_{CO_2}$  difference (stimulants), and lowering chemosensitivity (supplemental oxygen).<sup>34</sup> The pathophysiology of OSA and CSA is overlapping and not mutually exclusive. Treatment-emergent central apnea, also known as complex sleep apnea syndrome, describes the coexistence or appearance and persistence of central apneas/hypopneas often associated with periodic breathing in patients with coexistent OSA, with central apneas/hypopneas occurring frequently upon successful restoration of airway patency with continuous positive airway pressure (CPAP) therapy.<sup>33</sup>

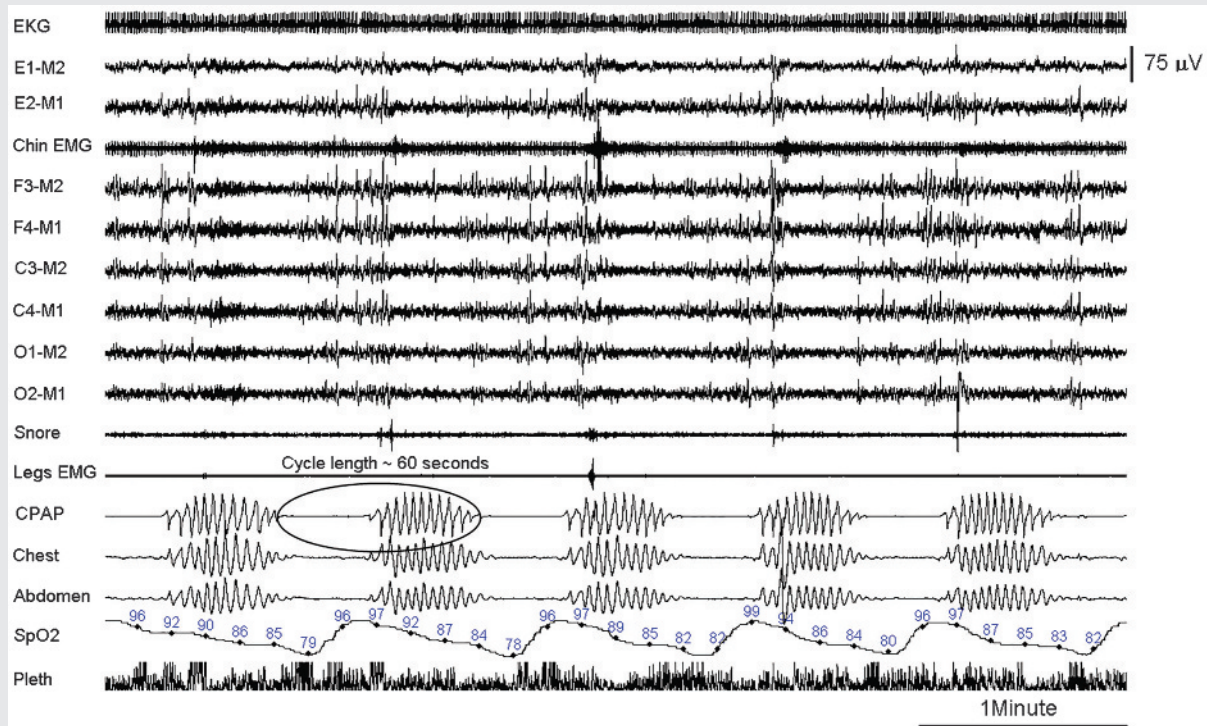
CSA is further differentiated by a hypercapnic or hypocapnic response. A hypercapnic response is caused by an impaired ventilatory output during wake, which further worsens during sleep. This impaired ventilatory output can be due to an impaired central drive (brainstem lesions, opioids, obesity hypoventilation syndrome, or congenital central alveolar hypoventilation syndrome) or impaired respiratory motor control (neuromuscular disorders, disorders of the autonomic nervous system, multiple system atrophy, motor neuron disease, cervical cordotomy, myopathies, or chest wall deformities). With opioid-induced CSA, central apneas are attributed to the inhibition of respiratory rhythmogenesis by mu receptor agonism in the pre-Bötzinger nucleus in the brainstem,<sup>35</sup> and opiate-dependent respiratory depression may also involve other structures in the brainstem respiratory network, including the parabrachial/Kölliker-Fuse complex of the pons, downstream bulbospinal neurons, and the phrenic motor nucleus.<sup>36</sup> In the case of respira-

tory motor control impairment, the central respiratory output is normal, but abnormalities are present within the pathway of the upper motor neurons to the muscles and chest cage. Opioid-induced CSA results in observed ataxic breathing in the form of irregular variations in the respiratory cycle length and tidal volume.

In contrast, CSA with a hypocapnic response manifests as Cheyne-Stokes respiration or primary CSA.<sup>37</sup> Cheyne-Stokes respiration is characterized by at least three consecutive central apneas or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 seconds, and at least five central apneas or central hypopneas per hour of sleep associated with a crescendo/decrescendo breathing pattern recorded over at least 2 hours of monitoring (Figure 9-5).<sup>2</sup> The pathophysiology in Cheyne-Stokes respiration involves a baseline hypocapnic state, resulting in minimal difference between the hypocapnic-apneic threshold and the sleeping eucapnic threshold, increased chemoreceptor responsiveness, hypoxia, state changes and arousals, upper airway instability, and prolonged circulation time (delay between lung blood and respiratory neuronal blood  $P_{aCO_2}$ ). When the  $P_{aCO_2}$  falls below the apneic threshold, an apnea is initiated, and the  $P_{aCO_2}$  begins to rise. The respiratory control center detects the increasing  $P_{aCO_2}$ , but with a delay due to the increased circulatory time. By the time the respiratory control center terminates the apnea, hypercapnia is present, which, in turn, stimulates robust hyperpnea, resulting in marked hypocapnia, permitting the cycle of events to repeat. An arousal typically occurs at the peak of the hyperpnea phase. The length of the central apnea is proportional to the reduction in  $P_{aCO_2}$ , while the hyperpnea and periodic

#### KEY POINTS

- Central sleep apnea with a hypercapnic response can be seen in disorders of impaired respiratory motor control, such as in neuromuscular disorders, autonomic nervous system disorders, multiple system atrophy, motor neuron disease, and myopathies.
- Central sleep apnea with a hypocapnic response can manifest as Cheyne-Stokes respiration, which, in the setting of heart failure, differs from other causes of periodic breathing by a significantly longer cycle length (more than 40 seconds), corresponding to a prolonged circulation time.

**FIGURE 9-5**

Cheyne-Stokes respiration. A 5-minute epoch illustrating cyclical central apneas with a crescendo-decrescendo breathing pattern associated with arousals and desaturations with a cycle length of 60 seconds (circled).

**KEY POINT**

- Sleep-related hypoventilation disorders manifest as insufficient ventilation, resulting in abnormally elevated  $\text{Paco}_2$  during sleep. Daytime awake hypoventilation, defined by a  $\text{Paco}_2$  of more than 45 mm Hg, may or may not be present. If daytime hypoventilation is present, it is further worsened during sleep.

breathing cycle length are proportional to the lung to carotid body circulation time and, inversely, to the cardiac output. The most important predisposing factors for Cheyne-Stokes respiration are comorbid congestive heart failure, stroke, and renal failure.<sup>1</sup> Cheyne-Stokes respiration due to heart failure differs from primary CSA and other causes of periodic breathing by a cycle length (beginning of a central apnea to the end of the next crescendo-decrescendo respiratory phase) of greater than 40 seconds, corresponding to the prolonged circulation time.

### Sleep-Related Hypoventilation and Hypoxemia

Sleep-related hypoventilation disorders manifest as insufficient ventilation, resulting in abnormally elevated  $\text{Paco}_2$  during sleep. Daytime awake hypoventilation, defined by a  $\text{Paco}_2$  of

more than 45 mm Hg, may or may not be present. If daytime hypoventilation is present, it is further worsened during sleep. On polysomnography, hypoventilation is defined as either an increase in the arterial  $\text{Pco}_2$  (or surrogate) to more than 55 mm Hg for at least 10 minutes, or a more than 10 mm Hg increase in arterial  $\text{Pco}_2$  (or surrogate) during sleep, compared to a value exceeding 50 mm Hg for at least 10 minutes when the patient is awake and supine.<sup>2</sup> The *ICSD-3* recognizes several disorders of hypoventilation, the most common of which is obesity hypoventilation syndrome.<sup>1</sup> Patients with obesity hypoventilation syndrome have a BMI of more than 30  $\text{kg/m}^2$  and experience alveolar hypoventilation while awake, which further worsens in sleep. Daytime symptoms include excessive daytime sleepiness, morning headaches,



mood disturbances, and memory or concentration impairment. Physical examination may suggest a fluid overload state. Evaluation typically reveals elevated serum bicarbonate and polycythemia, reduced forced vital capacity on pulmonary function testing, and echocardiographic findings of right ventricular hypertrophy, atrial enlargement, and ventricular dysfunction. Long-term consequences of chronic hypercapnia include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction.

Sleep-related hypoxemia is defined as an oxygen saturation during sleep of 88% or less in adults for at least 5 minutes in the absence of sleep-related hypoventilation on polysomnography, home sleep apnea testing, or nocturnal oximetry.<sup>1,2</sup> Concurrent OSA and CSA may be present, but are not thought to be the major cause of the hypoxemia. Physiologic causes such as known neuromuscular weakness from neuromuscular junction disorders or inherited neuropathies or myopathies should be considered. Hypoxemia may also be present while the patient is awake, but is typically most extreme in REM sleep because of reduced activation of the intercostal and accessory muscles, resulting in a greater ventilatory burden on the diaphragm. Chronic hypoxia can lead to polycythemia, pulmonary hypertension, heart failure, cardiac arrhythmias, and cognitive dysfunction.

### **Sleep-Disordered Breathing in Neurologic Disease**

Relative to other medical disorders, less attention is generally paid to the investigation of sleep and sleep therapies in the neurosciences. Yet, the role of sleep in the pathogenesis and treatment of several highly prevalent neurologic disorders associated with substantial morbidity and health care

costs is becoming increasingly recognized. The prevalence and treatment outcomes of sleep-disordered breathing have been most thoroughly investigated in patients with stroke and epilepsy; however, optimal screening methods have not been established.

Sleep apnea is a common, typically unrecognized risk factor for incident and recurrent stroke. An estimated 50% to 70% of patients with stroke have OSA,<sup>38</sup> and analysis of 3- and 10-year follow-up data from the Sleep Heart Health Study demonstrated a twofold to threefold increased risk for incident stroke in those with moderate to severe OSA.<sup>39</sup> OSA contributes to adverse effects after stroke, resulting in worse functional outcome, as well as longer hospitalization and increased mortality, and treatment with PAP therapy can improve recovery, although data are conflicting.<sup>40</sup> A recent study found that a revised STOP-BANG questionnaire incorporating BMI and age as continuous variables had a greater sensitivity of 0.94 (95% confidence interval, 0.89 to 0.98) and specificity of 0.60 (95% confidence interval, 0.49 to 0.71) in patients with stroke compared with the standard STOP-BANG, which had a sensitivity of 0.91 (95% confidence interval, 0.85 to 0.96) and a specificity of 0.48 (95% confidence interval, 0.37 to 0.60), underscoring the potential limitations of general screening instruments in chronic disease populations.<sup>41</sup>

Cheyne-Stokes respiration is also highly prevalent, affecting 10% to 40% of patients in the initial days following an acute stroke.<sup>38</sup> This periodic breathing pattern is associated with older age and worse stroke severity as well as comorbid cardiac disorders associated with a lower ejection fraction. Unlike OSA, Cheyne-Stokes respiration most commonly resolves within 1 to 3 months of acute stroke. Effects of

### **KEY POINTS**

- Patients with obesity hypoventilation syndrome have a body mass index of more than 30 kg/m<sup>2</sup> and experience alveolar hypoventilation while awake, which further worsens in sleep.
- Sleep-related hypoxemia is defined as an oxygen saturation during sleep of 88% or less in adults for at least 5 minutes in the absence of sleep-related hypoventilation on polysomnography, home sleep apnea testing, or nocturnal oximetry.
- An estimated 50% to 70% of patients with stroke have obstructive sleep apnea. Although Cheyne-Stokes respiration is highly prevalent in the initial days following acute stroke, it commonly resolves within 1 to 3 months of the acute stroke

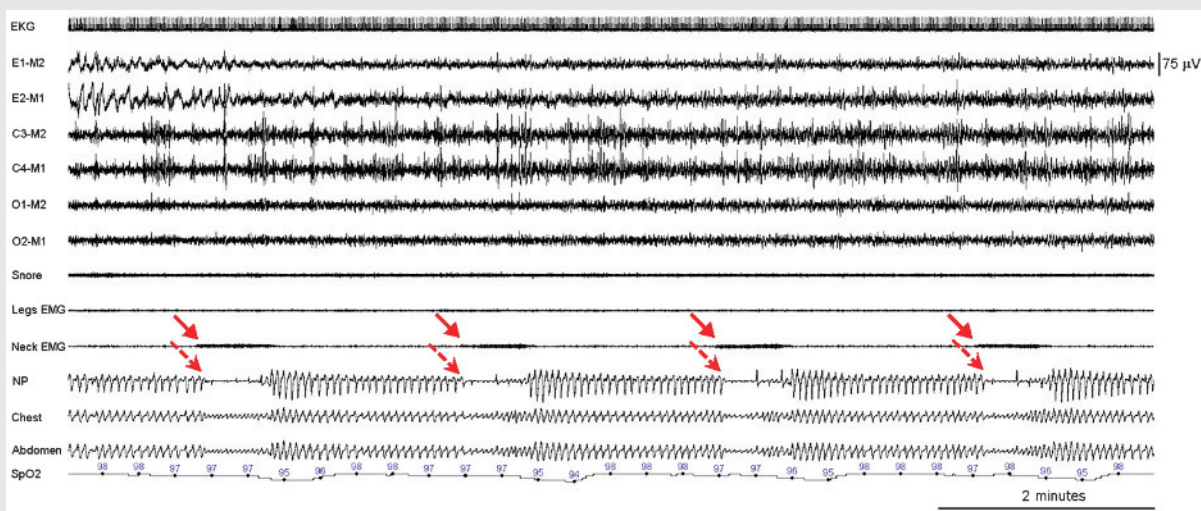


Cheyne-Stokes respiration on stroke risk are unclear and may be a consequence rather than a contributor to worsened outcomes. Central hypoventilation may be observed in the setting of brainstem and upper cervical cord ischemia. While adherence with sleep therapies is particularly challenging, sleep disorders are modifiable risk factors for stroke that should be routinely assessed in clinical practice.

Crucial links between sleep and epilepsy have been recognized for centuries. Despite surgical advances and an increasing number of new antiepileptic drugs, seizures remain uncontrolled in more than one-third of cases, increasing the risk of depression, academic and occupational underachievement, stigmatism, and sudden death. A recent meta-analysis reported a 33% prevalence of OSA in patients with epilepsy, which is twice that observed in healthy controls.<sup>42</sup> Prevalence rates in adults with epilepsy unselected for sleep disorder symptoms were 41% for an AHI of

5 or more per hour and 16% for an AHI of 15 or more per hour.<sup>43</sup> While prevalence did not differ based on seizure type, seizure frequency, or number of prescribed antiepileptic drugs, both age and standardized antiepileptic drug dose (a standardized variable of the total amount of antiepileptic drugs taken daily based on the assumed daily dose in its main indication assigned by the World Health Organization) were associated with OSA. Importantly, while more than 60% of patients reported excessive daytime sleepiness and more than 38% had abnormal Epworth Sleepiness Scale scores, neither was predictive of OSA.

Emergence or worsening of apneas and hypopneas has been reported in adults and children with epilepsy treated with vagus nerve stimulation (VNS) (**Figure 9-6**).<sup>44</sup> The underlying mechanisms are unclear, with both central and peripheral mechanisms proposed. Criteria for a diagnosis of OSA are met in as many as one-third of adult cases (**Case 9-1**). Lowering



**FIGURE 9-6**

Vagus nerve stimulation. A 10-minute polysomnographic epoch depicting repeated obstructive hypopneas (dashed arrows on nasal pressure [NP] channel) associated with oxygen desaturation coinciding with activation of vagus nerve stimulation. Stimulation artifact, as seen in the lateral neck EMG electrode (solid arrows), occurs at a consistent interval and duration. The respiratory events occur during stimulation and abruptly end with termination of stimulation.

## Case 9-1

A 25-year-old right-handed man with a history of epilepsy presented as a new patient to the epilepsy clinic. His seizures consisted of an indescribable visual disturbance evolving to unresponsiveness with staring, lip smacking, and unintelligible speech, followed rarely by right head version and a generalized tonic-clonic seizure. His seizures had persisted despite multiple medication trials. The patient's birth and development had been normal. He had had two concussions with brief loss of consciousness as a child, and he had undergone a tonsillectomy as a child.

A presurgical evaluation was conducted, including video-EEG monitoring and imaging studies. Generalized and left posterior quadrant spikes were recorded. Focal seizures demonstrating the features described above were recorded with nonlocalized EEG patterns. Mild bilateral hippocampal atrophy and left hippocampal dysmorphism were seen on MRI. Fludeoxyglucose positron emission tomography (FDG-PET) and ictal single-photon emission computed tomography (SPECT) demonstrated left parietotemporal changes. An invasive EEG evaluation recorded left lateral occipitotemporal spikes, but no seizures were captured.

After the inconclusive nature of his extensive presurgical evaluation, he was further considered for possible vagus nerve stimulator implantation. Further history then revealed that, for the last few years, he had developed disruptive snoring, occasional pauses in breathing, and increasing levels of daytime sleepiness.

Upon referral to the sleep clinic, examination was notable for a body mass index of 30 kg/m<sup>2</sup>, a neck circumference of 42 cm, and a Friedman grade III tongue position. A sleep history revealed frequent night awakenings, snoring, and dozing in sedentary situations. He had gained 14 kg (30 lb) in the last 6 months after loss of his job, and he felt depressed. Polysomnogram revealed obstructive sleep apnea (OSA) (an apnea-hypopnea index of 17 per hour, an arousal index of 20 per hour, and an oxygen saturation nadir of 67%).

Treatment with continuous positive airway pressure (CPAP) of 10 cm H<sub>2</sub>O abolished snoring and respiratory events and maintained oxygen saturations above 93%. Seizures began to decline after CPAP therapy at home. Within months, vagus nerve stimulation (VNS) implantation ensued, and he became entirely seizure free for the next 8 years, despite a lead fracture and battery failure. After 10 years of VNS and CPAP therapy, daytime sleepiness and rare breakthrough seizures recurred, prompting repeat titration, resulting in a CPAP pressure increase to 16 cm H<sub>2</sub>O.

**Comment.** The case illustrates the benefits of OSA therapy in patients with epilepsy. A sleep history was solicited only after the patient had completed an extensive evaluation, including invasive EEG. Seizures began to improve even before VNS implantation once CPAP therapy was initiated. Despite two lapses in VNS therapy over time, seizure control was maintained. Emergence or worsening of apneas and hypopneas coinciding with VNS activation has been reported in adults and children with epilepsy. Screening for OSA and consideration of polysomnography prior to and following VNS implantation is recommended.

# KEY POINTS

- Because of emergence or worsening apneas and hypopneas coinciding with vagus nerve stimulation therapy in patients with epilepsy, screening for obstructive sleep apnea and consideration of polysomnography prior to and following device implantation is recommended.
- In-laboratory polysomnography is the gold standard for the evaluation of sleep-disordered breathing and can be tailored to the clinical history (ie, expanding EEG/EMG for the evaluation of seizures and parasomnias) or combined with therapeutic titration of positive airway pressure, oxygen, oral appliances, or hypoglossal nerve stimulation.
- Home sleep apnea testing is indicated for the confirmation of obstructive sleep apnea in patients with presumed moderate to severe obstructive sleep apnea, but should not be used to screen asymptomatic patients, those with suspected mild obstructive sleep apnea, or in patients with significant comorbid medical conditions, suspected central sleep apnea, or sleep-related hypoventilation.

stimulation frequencies or prolonging off-time may prevent OSA exacerbations. The device manufacturer recommends screening for OSA and considering polysomnography prior to and following VNS implantation. Based on retrospective series, treatment of OSA in patients with epilepsy, using CPAP therapy in adults or tonsillectomy in children, has been shown to reduce seizure frequency and interictal epileptiform discharges, alleviate daytime sleepiness, and improve sleep quality, depressive symptoms, and quality of life.<sup>45,46</sup>

Both OSA and CSA as well as sleep-related hypoventilation and hypoxia are observed in patients with neuromuscular disorders, such as amyotrophic lateral sclerosis, myasthenia gravis and Lambert-Eaton myasthenic syndrome, inherited myopathies such as myotonic dystrophy, and muscular dystrophies, although prevalence is uncertain.<sup>47</sup> Affected patients are at risk for sleep-disordered breathing because of a combination of factors including muscle weakness, damage to central nervous system respiratory control centers, medication side effects, and weight gain due to inactivity.

# LABORATORY TESTING

Sleep testing in the sleep laboratory (polysomnography) or at home (home sleep apnea testing) is required to confirm the diagnosis of sleep-related breathing disorders. In-laboratory polysomnography is the gold standard for the evaluation of sleep-disordered breathing and can be tailored to the clinical history (ie, expanding EEG/EMG for the evaluation of seizures and parasomnias) or combined with therapeutic titration of PAP (Figure 9-7), oxygen, oral appliances, or hypoglossal nerve stimulation. Polysomnography includes EEG and body position, allowing for the comparison of the AHI between

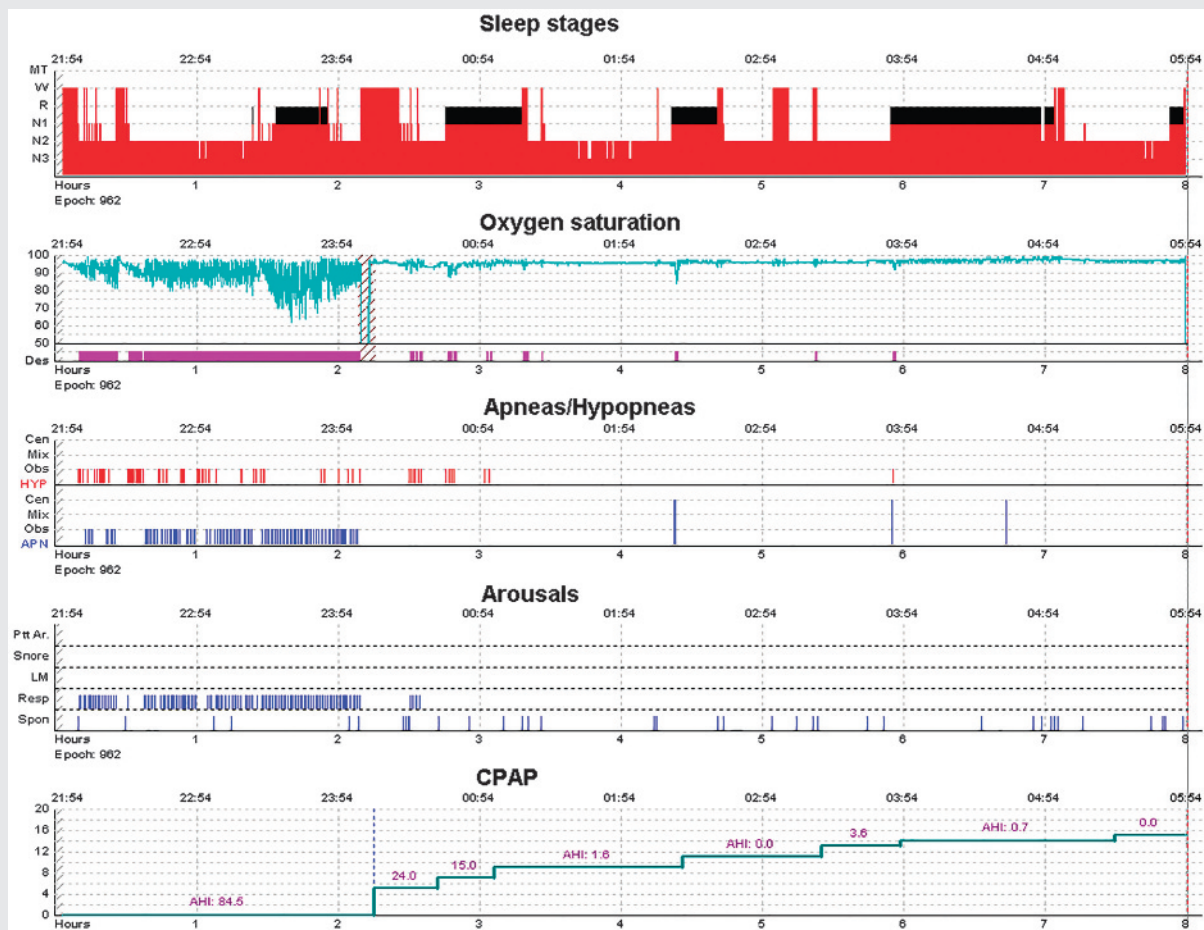
REM and non-REM sleep and supine or nonsupine sleep positions.

By contrast, home sleep apnea testing is limited to the recording of airflow, nasal pressure, respiratory effort, ECG, and oxygen saturation. Therefore, home sleep apnea testing may underestimate the severity of sleep-disordered breathing because of the inability to score hypopneas associated with arousal and may overestimate sleep time since it is unknown what extent of recording time represents actual sleep time (Figure 9-8).<sup>48</sup> Home sleep apnea testing is indicated in adults 18 to 65 years of age, with a high pretest probability for moderate to severe OSA in the absence of comorbid sleep or medical disorders that compromise the test's accuracy, and in those who otherwise could not complete a polysomnogram because of safety, immobility, or critical illness, including some individuals with moderate to severe pulmonary disease, neuromuscular disease, heart failure, and comorbid sleep disorders such as insomnia, suspected CSA, and sleep-related hypoventilation. Home sleep apnea testing is not recommended for screening asymptomatic populations or for those with suspected mild OSA severity; false-negative home sleep apnea tests have been observed in up to 17% of patients with moderate to severe OSA.<sup>48</sup> Consequently, repeat home sleep apnea tests or polysomnography should be considered in patients with a high pretest probability and a negative home sleep apnea test. Nocturnal pulse oximetry is not recommended for the evaluation of suspected OSA or other forms of sleep-disordered breathing due to its low sensitivity and specificity.

# SLEEP-DISORDERED BREATHING TREATMENT AND OUTCOMES

Treatment of OSA is geared toward reducing the critical closing pressure





**FIGURE 9-7** Hypnogram of a split-night polysomnogram illustrating sleep stages, respiratory events by type, oxygen saturation, and positive airway pressure settings. The apnea-hypopnea index during the diagnostic portion was 85 per hour, normalizing with positive airway pressure settings of 9 cm H<sub>2</sub>O, 11 cm H<sub>2</sub>O, and 13 cm H<sub>2</sub>O to 15 cm H<sub>2</sub>O, including supine rapid eye movement (REM) sleep (captured at positive airway pressure settings 13 cm H<sub>2</sub>O to 15 cm H<sub>2</sub>O), where events were most resistant.

of the upper airway to maintain airway patency, thereby restoring sleep quality and eliminating daytime symptoms and long-term medical consequences. The following general therapeutic measures should be incorporated into the management strategy of all patients with OSA: (1) weight loss for overweight patients; (2) avoidance of alcohol and other central nervous system depressants before bed; (3) encouraging nonsupine sleep positioning; (4) treatment of nasal congestion or fixed obstructions, which can contribute to reduced PAP adherence

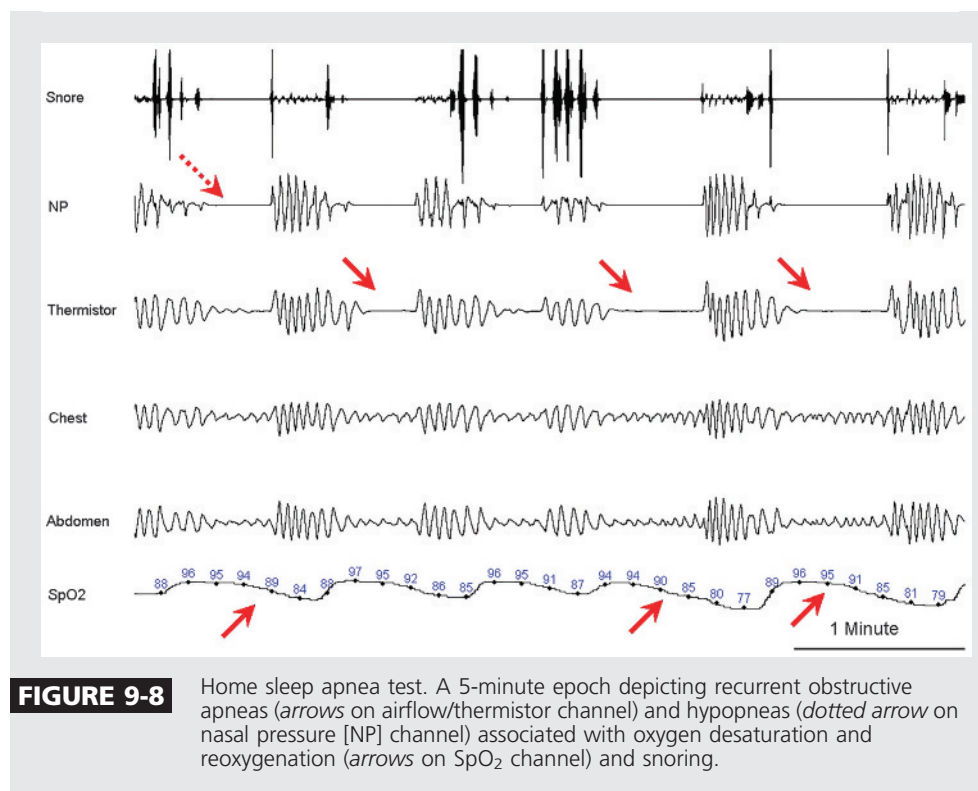
due to pressure intolerance and mask leaks; and (5) screening as indicated for hypothyroidism, polycystic ovary syndrome, and acromegaly, because specific treatment of these disorders can significantly alleviate or even reverse OSA.

### Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation refers to the application of positive pressure during the respiratory cycle, the simplest and most commonly used modality for OSA

# KEY POINT

■ Noninvasive positive pressure ventilation is the gold standard treatment for sleep-disordered breathing. Different delivery modes are available to enhance effectiveness and adherence, the most common modality for obstructive sleep apnea being continuous positive airway pressure.



**FIGURE 9-8** Home sleep apnea test. A 5-minute epoch depicting recurrent obstructive apneas (arrows on airflow/thermistor channel) and hypopneas (dotted arrow on nasal pressure [NP] channel) associated with oxygen desaturation and reoxygenation (arrows on SpO<sub>2</sub> channel) and snoring.

being CPAP through the respiratory cycle. CPAP delivers the same set pressure throughout the respiratory cycle during spontaneous breathing, acts as a pneumatic splint, and allows the pressure within the collapsible airway to rise above atmospheric and pharyngeal critical closing pressure, thereby maintaining airflow. Numerous modes of noninvasive ventilation are available, with techniques that control how the delivery of pressure (mechanical breaths) is started (triggered), controlled (targeted), and ended (cycled).<sup>49</sup>

More sophisticated levels of PAP therapy are indicated for patients with OSA who have an inadequate response to CPAP, pressure intolerance, interface leak, hypoventilation, or persistent hypoxia. Bilevel PAP (BiPAP) administers two different levels of pressure, one for inspiration and one for expiration, effectively decreasing the amount of pressure against which the patient exhales, thereby decreasing

abdominal muscle recruitment and discomfort during the expiratory cycle. Additional indications for BiPAP include sleep-disordered breathing associated with heart failure, neuromuscular disease, restrictive pulmonary disease, CSA, complex sleep apnea syndrome, and hypoventilation syndromes including obesity hypoventilation syndrome.<sup>49</sup> The addition of a back-up rate is often required in the setting of hypoventilation.

Auto-titrating PAP devices (auto-CPAP, auto-BiPAP) use proprietary self-adjusting algorithms to detect variations in airflow resulting from varying levels of obstruction and, consequently, adjust the pressure level to restore normal breathing. These devices can help to compensate for various factors that modify upper airway collapsibility, such as body posture, sleep stage, and use of alcohol, sedative hypnotics, and other drugs that affect upper airway muscle tone.<sup>49</sup>



Auto-CPAP is not recommended in making the diagnosis of OSA, is not meant for use in patients who do not snore, and is not meant for the treatment of CSA or nocturnal desaturation due to disorders other than OSA, including hypoventilation syndromes.<sup>50</sup>

The beneficial effects of PAP therapy have been demonstrated largely in observational and retrospective studies involving patients with moderate to severe OSA. CPAP therapy improves quality of life by reducing daytime sleepiness, depressed mood, cognitive impairments, as well as motor vehicle and occupational accidents. CPAP also may improve glycemic control and decrease cardiovascular (myocardial infarction or stroke) events and mortality, although robust treatment effects have not been consistently demonstrated in limited randomized clinical trials.<sup>51–54</sup>

Two commonly used specialized modalities of BiPAP therapy used in central apnea and hypoventilation syndromes include adaptive servo-ventilation and volume-assured pressure support. Adaptive servo-ventilation therapy is approved for use in patients with CSA, complex sleep apnea, and Cheyne-Stokes respiration. This device adjusts the degree of pressure support for each inspiration with a goal to maintain a moving target ventilation set at 90% of the patient's recent average ventilation.<sup>49</sup> The aim is to stabilize breathing and reduce respiratory alkalosis; this can trigger apnea reentry cycles, which are often part of the pathogenesis of CSA and Cheyne-Stokes respiration in patients with heart failure or complex sleep apnea syndrome. The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo-ventilation in Patients with Heart Failure (SERVE-HF) trial, involving 1325 patients with a left ventricular ejection fraction of 45% or less, an AHI of 15 or

more per hour, and with a predominance of central events, reported increased mortality with adaptive servo-ventilation despite adequate control of respiratory events, leading to study termination.<sup>55</sup> However, analysis of the composite primary end point (time to first event or death from any cause, life-saving cardiovascular intervention, or unplanned hospital admission for worsening heart failure) was neutral. In contrast to adaptive servo-ventilation, volume-assured pressure support is the preferred mode for hypoventilation disorders including obesity hypoventilation syndrome, neuromuscular disorders, and primary lung diseases such as chronic obstructive pulmonary disease. This mode allows for variance within the inspiratory pressure to achieve a set target tidal volume without breath-by-breath changes that enhances patient comfort.

Current PAP technologies can deliver data output from device to provider to confirm adherence and monitor for residual respiratory events and enable troubleshooting for interface leak and pressure complaints. Federal Medicare and some private payer regulatory requirements generally stipulate minimum device use of 4 hours for 70% of nights in the initial 90 days of PAP usage for continued coverage of the device and ancillary supplies. Using this definition of adherence, as many as 46% to 83% of patients with OSA are reported to be nonadherent to treatment.<sup>56</sup> Optimal adherence requires timely troubleshooting and repeated education and support of the patient and bed partner over time.

### Alternative Treatments

Many options for surgical intervention of OSA exist, including surgical weight loss and soft tissue and skeletal structure interventions. Bariatric surgery

#### KEY POINT

- Positive airway pressure device reimbursement requires patient compliance with the device for a minimum of 4 hours for 70% of nights in the 90 days after initiating therapy.

improves or eliminates OSA in more than 75% of cases.<sup>57</sup> Surgical modifications of the upper airway have been performed for decades; however, high-level randomized controlled studies are limited, and more than 30 different techniques have been reported.<sup>58</sup> Outcomes of sleep surgeries are highly variable, and multilevel simultaneous or phased surgeries combined with uvulopalatopharyngoplasty are often necessary. A recent meta-analysis reported surgical cure (residual AHI of less than 5 per hour) in 38.5% and surgical success (more than 50% AHI reduction to fewer than 20 events per hour) in 85.5% following maxillary mandibular advancement, a procedure that expands the facial skeletal framework, enlarging the nasopharyngeal, retropalatal, and hypopharyngeal airway.<sup>59</sup> Lower preoperative AHI was associated with a greater likelihood of surgical success or cure.

Hypoglossal nerve stimulation is the newest surgical treatment for OSA. It is used in adults 22 years of age or older who have a BMI of less than 32 kg/m<sup>2</sup> and an AHI of 20 to 65 per hour with less than 25% central or mixed events, in patients proven to fail or be intolerant of PAP therapy, and in patients who do not have complete concentric collapse of the soft palate during drug-induced sleep endoscopy. The development of hypoglossal nerve stimulation as a therapeutic option stems from evidence that stimulation of the genioglossal muscle, the primary pharyngeal dilator, or the hypoglossal nerve could reverse inspiratory flow limitation during sleep.<sup>60</sup> Hypoglossal nerve stimulation is an implanted system consisting of a thoracic respiratory sensing lead, a pulse generator, and the electrode cuff that has been found to increase the oropharyngeal airway, as well as the retropalatal airway, through tongue protrusion and palatoglossal

coupling.<sup>61</sup> In the multicenter pivotal trial, stimulation led to significant improvements in objective and subjective measurements of OSA severity, including a reduction in median AHI of 68%, improved quality of life, and average nightly compliance exceeding 80%, with few unanticipated adverse events.<sup>60</sup>

In recent years, oral appliance therapy has become an increasingly popular treatment for snoring and OSA. A variety of types and styles are available, which are fabricated and titratable under the supervision of a qualified dentist, while over-the-counter boil-and-bite devices are not recommended. Oral appliances are intended to protrude and stabilize the mandible, increasing retropalatal and retrolingual airway patency during sleep. While oral appliances effectively reduce the frequency and intensity of snoring, improve sleep quality for patients who snore and their bed partners, and improve quality of life measures in snorers, evidence for their effectiveness in OSA is limited.<sup>62</sup> Meta-analyses using limited available evidence indicate that oral appliances can significantly reduce the AHI across all levels of OSA severity in adults, with no significant difference compared with CPAP in patients with mild OSA; however, the odds of achieving a target AHI are significantly greater with CPAP in patients with moderate to severe disease.<sup>62</sup> Generally, favorable candidates for oral appliance therapy include younger patients and those with a lower BMI, smaller neck circumference, lower AHI, and supine positional dependency of obstructive events. Contraindications include active or recent orthodontics, periodontal compromised dentition, temporomandibular joint dysfunction, and uncontrolled seizure disorders. The most common side effects include dental occlusal changes, excess salivation or

dry mouth, jaw discomfort, and tooth tenderness. These devices offer advantages over PAP in that they do not require a source of electricity and are less cumbersome, especially during travel.

Expiratory PAP therapy is an expiratory resistance device consisting of mechanical valves with low inspiratory resistance but high expiratory resistance applied to the nares with an adhesive seal before sleep. The high expiratory resistance results in positive pressure throughout exhalation, which acts to splint the upper airway, rendering it more resistant to collapse on subsequent inspiration.<sup>63</sup> Limited evidence suggests that snoring, AHI, and desaturations improve in some cases. Long-term efficacy in optimal candidates is unknown. Nasal patency is required. Difficulty with exhaling, nasal discomfort, dry mouth, headache, and insomnia have been reported. Like oral appliance therapy, expiratory PAP therapy is appealing for patients who travel and those with mild OSA without significant medical comorbidities who might go without PAP therapy for short periods.

Oral pressure therapy is a system that creates an oral vacuum with a pump console that is connected to a premanufactured polymer mouthpiece with flexible tubing that stabilizes the tongue and produces anterior movement of the soft palate, thereby increasing the airway in both the anterior-posterior and lateral dimensions. In a single randomized trial, AHI, oxygen desaturations, and Epworth Sleepiness Scale scores improved in one-third of users.<sup>64</sup> Oral tissue discomfort or irritation, dental discomfort, and dry mouth were reported.

## CONCLUSION

Sleep-disordered breathing is highly prevalent and grossly underrecognized. The adverse medical and psychosocial

consequences of OSA and other sleep-related breathing disorders are considerable. The impact of PAP therapy on highly prevalent neurologic disorders including stroke and epilepsy is becoming increasingly recognized. Recent advances in the treatment of OSA have resulted in effective PAP alternatives in some cases. Long-term treatment of sleep-disordered breathing has a favorable impact on many medical comorbidities, most notably, cardiovascular diseases. The impact of sleep therapies on long-term outcomes in neurologic populations remains to be elucidated.

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# Comorbid Sleep Disturbances in Neurologic Disorders

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## ABSTRACT

**Purpose of Review:** This article provides a review of disturbances of sleep comorbid with common neurologic disorders.

**Recent Findings:** A wide variety of neurologic disorders are frequently complicated by comorbid sleep disturbances. In many cases, a bidirectional relationship appears to occur between sleep function and the neurologic disease, such that treatment of comorbid sleep disturbances may improve the symptoms of the neurologic disease.

**Summary:** Neurologic disorders are often associated with abnormalities of sleep. Sleep influences the severity of both epilepsy and headache, and treatment of comorbid sleep disorders may improve seizure and headache frequency. Alzheimer disease is characterized by circadian phase delay and poor nighttime sleep and is strongly associated with obstructive sleep apnea. Parkinson disease is associated with several sleep disorders, including insomnia, restless legs syndrome, rapid eye movement (REM) sleep behavior disorder, daytime hypersomnia, and sleep-disordered breathing. Hypoventilation in amyotrophic lateral sclerosis and other neuromuscular disorders often presents initially with sleep problems, and treatment with noninvasive ventilation improves survival and quality of life.

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## INTRODUCTION

Sleep is a complex brain-generated behavior. Therefore, unsurprisingly, neurologic diseases frequently are associated with sleep disturbances. This article discusses the most commonly encountered comorbid sleep disorders in neurologic practice, with particular attention to the interaction between sleep function and neurologic disease. The article details sleep disorders in epilepsy, headache, Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS). Key sleep-related features in neurologic disorders are summarized in Table 10-1.

## SLEEP AND EPILEPSY

Sleep provides an opportunity to examine and potentially improve epilepsy. A variety of physiologic repercussions of sleep influence the electric and pathophysiologic manifestations of epilepsy. These range from promotion or inhibition of epileptic events to the theoretic effects of kindling in epileptic pathophysiology. In addition, epilepsy can cause further sleep disruption and changes in sleep architecture. Likewise, the treatment of epilepsy can impact sleep. These dynamic relationships lead to patients with epilepsy frequently having sleep problems.

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**TABLE 10-1 Common Comorbid Sleep Comorbidities in Neurologic Diseases**

Neurologic Disease	Common Sleep Comorbidities	Common Presenting Symptoms	Targeted Investigations	Treatments and Notes
Epilepsy	Insomnia, obstructive sleep apnea	Sleep fragmentation	Polysomnography with full EEG and video	Treat underlying seizure disorder
Headache	Insomnia, obstructive sleep apnea	Sleep fragmentation	Polysomnography	Treat sleep apnea, improve sleep hygiene (see Table 10-2 for specific syndromes)
Alzheimer disease	Obstructive sleep apnea, delayed circadian phase	Snoring, apneas, sundowning, nighttime wandering, daytime sleepiness	Polysomnography, actigraphy	Positive airway pressure if obstructive sleep apnea
Parkinson disease	Insomnia, rapid eye movement sleep behavior disorder, restless legs syndrome, hypersomnia, sleep-disordered breathing	Early morning awakenings, dream enactment, restless legs, daytime sleepiness	Polysomnography with video EEG	Adjust Parkinson disease medications, melatonin/clonazepam
Neuromuscular disorders	Hypoventilation, obstructive sleep apnea	Orthopnea, morning headache, hypersomnia, sleep fragmentation	Oximetry, polysomnography, pulmonary function tests, arterial blood gas	Volume-targeted noninvasive ventilation or bilevel positive airway pressure (see Table 10-3 for specific disorders)
Stroke	Obstructive sleep apnea and central apneas	Snoring, witnessed apneas, hypertension	Polysomnography	Central sleep apnea may resolve in the immediate poststroke period
Multiple sclerosis	Obstructive sleep apnea, restless legs syndrome	Multiple sclerosis–related fatigue	Polysomnography	Sleep disorders are associated with cognitive dysfunction

EEG = electroencephalogram.

# KEY POINT

- Seizures are more likely to start during non-rapid eye movement sleep, whereas rapid eye movement sleep appears to be protective against seizures.

The influence of sleep can be examined by the effect of total sleep and the effect of each stage. Since Hippocrates, patients with epilepsy have been warned to avoid sleep deprivation, and several studies show the provocative nature of sleep deprivation on epileptic events.<sup>1</sup> In addition, oversleeping appears to increase the occurrence of epileptic seizures.<sup>2</sup> Although no good

selective sleep stage deprivation studies have been performed in humans, studies in animals suggest the selective loss of rapid eye movement (REM) sleep may enhance the kindling process and cause progression in intractability of focal-onset seizures.<sup>3</sup> Likewise, the sleep stage may influence seizure onset. Seizures are more likely to start during non-REM sleep, whereas REM

sleep appears to be protective against seizures.<sup>4</sup> Similarly, interictal discharges are more likely in non-REM sleep, with the greatest increase in frequency, topography, and localization noted with the approach of deeper stages of non-REM sleep.<sup>5</sup> REM sleep is the state least likely to have interictal discharges, and these discharges are most restricted to near the epileptic focus; thus, REM sleep offers an opportunity for better localization of epileptic foci.<sup>6</sup> Although these observations are clear, the underlying reason for the difference of topography of the interictal discharges is still somewhat unclear. Most theories rest on the hypothesis that more neurons are in the resting state in non-REM sleep and thus are available for recruitment into the discharge; however, during REM sleep, overall greater neuronal firing occurs, and neurons are less available to be recruited into the interictal firing.

Some epilepsies are specifically related to sleep.<sup>6</sup> Benign epilepsy of childhood with central temporal spikes is typically associated with seizures manifesting as focal spasms of the face or hand with jerking, occurring in the first one-third of the night. These events classically start in non-REM sleep and, for many patients, the interictal discharge appears only during sleep. Similarly, autosomal dominant nocturnal frontal lobe epilepsy is also seen as a variety of brief and occasionally violent hyperkinetic events occurring from non-REM sleep. This disorder is associated with an abnormality in the nicotinic receptor complex, and seizures may be frequent and often occur only during sleep. These patients appear to respond to carbamazepine or lamotrigine; however, a portion remains intractable. Other epilepsy syndromes such as Panayiotopoulos syndrome and Landau-Kleffner syndrome are also associated with nocturnal events

or discharges. Some primary generalized epilepsies, especially those including myoclonus, are associated with seizures soon after awakening, indicating that seizure generation is somehow more prominent during the sleep-to-wake transition period.

Epilepsy also produces changes in sleep. Seizures are noted to cause postictal somnolence, but also evoke more wake after sleep onset, sleep fragmentation, and REM sleep suppression during the sleep period following the seizure. This effect appears to extend beyond frank seizures. Interictal discharges also cause sleep fragmentation, potentially by disrupting signals involved in sleep circuitry, thus disrupting the physiologic coordination of sleep. This disruption may have some downstream effect as it has been hypothesized that nighttime discharges may influence daytime learning.<sup>7</sup> Recent studies have shown correlations between nighttime seizure activity and complaints of nighttime disruption and daytime symptoms.<sup>8</sup> Similarly in adults, patients with frequent interictal discharges during sleep had more daytime symptoms of sleepiness, and antiepileptic drugs may help decrease the frequency of nocturnal discharges and improve daytime symptoms.<sup>6</sup>

Nearly two-thirds of patients with epilepsy note sleep problems.<sup>6</sup> These symptoms translate into a higher prevalence of underlying sleep issues. Polysomnographic examination of patients with epilepsy showed a high prevalence of obstructive sleep apnea (OSA), a disorder in which the upper airway collapses during sleep, often accompanied by sleep fragmentation.<sup>9</sup> Diagnosis and treatment of comorbid sleep apnea may offer an opportunity to improve seizure frequency and quality of life in patients with epilepsy. Several case series and one randomized double-blind trial have shown that

#### KEY POINT

- Diagnosis and treatment of comorbid sleep apnea may offer an opportunity to improve seizure frequency and quality of life in patients with epilepsy.

**KEY POINTS**

- Sleep deprivation and excessive sleep increase headaches in both children and adults.
- Hypnic headaches (sometimes called alarm clock headaches) abruptly awaken patients after 1 to 3 hours of sleep and may respond to caffeine or, if frequent, treatment with lithium.

addressing comorbid sleep problems was associated with improvement in intractable epilepsy.<sup>6</sup>

Many medications used to treat epilepsy influence sleep, yet most need further study in both patients with epilepsy and in normal controls. Traditional medications such as phenobarbital, carbamazepine, phenytoin, and valproate have a soporific effect, but they also may produce significant changes in overall sleep architecture, such as decreased REM sleep or increased sleep fragmentation. Pregabalin and gabapentin both appear to have a benefit by increasing slow-wave sleep and may improve sleep and attention in patients with epilepsy and insomnia.<sup>6</sup> Some medications such as felbamate, zonisamide, or lamotrigine at high doses may cause insomnia. At lower doses, lamotrigine and levetiracetam appear to have little overall effect on sleep. The overall downstream influence of these medications on sleep and, possibly, on the epileptic focus during sleep, still needs to be studied. Preliminary work suggests that chronopharmacology, adjusting so that sedating medications have higher doses at night, may improve seizure response and lower incidence of side effects.<sup>6</sup>

**SLEEP AND HEADACHES**

Headaches, similar to epileptic seizures, share a complex bidirectional relationship with sleep. Although both headaches and sleep issues may be common and occur in the same patient, the relationship of sleep to headaches appears to be more than coincidental. Sleep disruption can predispose, provoke, and perpetuate headache issues, whereas sleep may also improve headaches. In general, sleep deprivation and excessive sleep increase headaches in both children and adults.<sup>10</sup> For patients predisposed to headaches, the link to

sleep is even greater. Nearly 86% of patients with episodic migraine note poor sleep quality, and poor sleep was associated with increasing headache frequency and headache-related disability.<sup>11</sup> Likewise, poor sleep hygiene was noted as a frequent perpetuating agent in transformed migraine, and the improvement of sleep-promoting behaviors reverted the transformed migraine back to episodic migraine.<sup>12</sup>

This relationship between headaches and sleep extends to those with primary sleep disorders. Patients with insomnia have a 50% greater likelihood of having headaches and more severe headaches. Similarly, bed partners of habitual snorers are also more likely to have headaches, suggesting the environmental disturbance of sleep makes headaches more likely.<sup>10</sup> Also, 15% to 60% of patients with OSA report headaches, and these individuals are more likely to develop morning headache, migraine, chronic headache, and tension-type headaches.<sup>10,13</sup> Yet, treatment of sleep apnea with continuous positive airway pressure (CPAP) appears to improve headache frequency and intensity.<sup>10,14</sup> The interaction of headaches, sleep, and epilepsy is illustrated in **Case 10-1**.

Some headache types emerge from specific stages of sleep (**Table 10-2**), indicating sleep may set the neurochemical stage to initiate the headache.<sup>14</sup> Cluster headaches typically emerge during REM sleep. Migraine headaches that awaken a patient from sleep are more likely to be associated with vivid dreaming, suggesting they may arise during REM sleep; however, further studies are needed. Hypnic headaches (sometimes called alarm clock headaches) abruptly awaken patients after 1 to 3 hours of sleep and may respond to caffeine or, if frequent, treatment with lithium. Chronic paroxysmal hemicrania also may awaken patients



## Case 10-1

A 27-year-old woman with static encephalopathy and focal-onset seizures presented with an 8-month progressive increase in her seizures. The patient previously had averaged approximately one seizure every 6 months, which had recently increased to two seizures per month. The intensity and duration of the seizures also appeared to have increased. The patient was being treated with lamotrigine 500 mg/d and previously had experienced no side effects. On presentation, she reported morning headaches, and the family noted that the patient fell asleep in the afternoon at the workshop where she spent most of her days. In review of her other symptoms, the family noted that the patient had had a 9 kg (20 lb) weight gain over the last 2 years, and the patient had begun snoring at night. The patient had an elevated Epworth Sleepiness Scale score of 11. An overnight sleep study revealed moderate obstructive sleep apnea with an apnea-hypopnea index of 17 per hour and events that had oxygen desaturation to 85%.

Although initially the patient had difficulty adjusting to continuous positive airway pressure (CPAP), the patient and family incorporated positive behavior modification techniques that resulted in the patient wearing the CPAP on a nightly basis. After 3 months of therapy, the patient had only one seizure, and the daytime sleepiness and morning headaches had resolved.

**Comment.** Sleep difficulties are a common aggravator of both epileptic seizures and headaches. This case demonstrates a patient with both increasing seizures and the development of headaches. However, either of these symptoms should be a clue to the clinician to ask about sleep issues. This case also demonstrates how the treatment of sleep issues such as obstructive sleep apnea may improve underlying neurologic conditions such as epilepsy or headaches.

suddenly from sleep with abrupt clawing pain, and these events respond well to indomethacin.<sup>14</sup> Despite the current lack of pathophysiologic understanding, both the mechanisms for sleep and headache generation share some of the same hypothalamic and brainstem circuitry, and improvement in sleep offers a unique pathway to improve headache care.

### SLEEP DISTURBANCES IN ALZHEIMER DISEASE

Sleep-wake and circadian disturbances start early in AD and increase in prevalence and severity as AD progresses. Even at the earliest presymptomatic or preclinical stage of AD, a bidirectional association exists between sleep disturbance and AD pathology.<sup>15</sup> A candidate mechanism by which sleep may af-

fect long-term AD risk is that sleep, particularly non-REM sleep, decreases amyloid- $\beta$  through decreased production and increased glymphatic clearance.<sup>16,17</sup> Therefore, sleep disruption is predicted to increase amyloid- $\beta$  levels and, over time, increase risk of insoluble amyloid plaque formation, the first known step in AD pathogenesis.

Sleep-wake disturbances bothersome to caregivers are present in approximately 40% of community-dwelling patients with symptomatic AD<sup>18</sup> and occur around the clock. While typically a circadian phase advance occurs with aging, AD is associated with a circadian phase delay.<sup>19</sup> This phase delay probably contributes to sundowning (ie, restlessness, confusion, and agitation in the evening) that is difficult to treat and creates

**TABLE 10-2** Sleep-Related Headaches

Headache Type	Pain Description	Possible Sleep Association	Treatment
Cluster headache	Short, excruciating, lancinating pain behind one eye with autonomic features such as red conjunctiva, dilated pupil, swelling around the eye, rhinorrhea, or ptosis; each episode lasts 15–180 minutes	May occur near rapid eye movement (REM) sleep	Oxygen, triptans, verapamil, valproate, lithium
Hypnic headache	No autonomic symptoms, typically short duration but lasts for 15–180 minutes after waking	Awaken patient suddenly from sleep at similar time each night, typically at 1:00 AM to 3:00 AM	Caffeine, lithium
Paroxysmal hemicrania	Unilateral, severe, throbbing clawlike boring on the side of the head, accompanied by autonomic symptoms	Can occur out of sleep and last 2–45 minutes	Indomethacin
Sleep apnea headache	Bilateral pressing quality	Present upon awakening, resolves in approximately 30 minutes	Positive airway pressure

**KEY POINTS**

- Common sleep-wake disturbances in Alzheimer disease include nighttime insomnia, evening sundowning, and daytime sleepiness. Nighttime wandering raises safety concerns and increases caregiver burden and, therefore, is a common reason for institutionalization.
- Obstructive sleep apnea is very common in patients with Alzheimer disease, and treatment may improve cognitive symptoms.

substantial caregiver distress. Insomnia at night may lead to wandering and subsequent risk of falls or injury and therefore is a frequent reason for institutionalization. During the daytime, patients with AD may have excessive sleepiness, preventing engagement in social events and therapies, while increasing the risk of driving accidents.

OSA is particularly common in AD, is present in 40% of community-dwelling patients with AD, is present in up to 70% of those with AD in the institutionalized setting,<sup>20,21</sup> and may contribute to cognitive symptoms. Since treatment of OSA may be helpful in ameliorating cognitive decline in AD,<sup>22</sup> symptoms such as snoring, daytime sleepiness, or witnessed apneas should prompt evaluation for OSA.

The American Academy of Neurology (AAN) Dementia Measures Work Group defined dementia management quality

measures specifically addressing sleep and circadian disturbances under neuropsychiatric symptom assessment, as well as a part of depressive symptom screening.<sup>23</sup> Additionally, given the growing literature on the effect of sleep-wake disturbances in AD, sleep-wake functioning should be included as part of assessing safety/driving risks and caregiver education. Unfortunately, no specific treatments exist for sleep disorders in AD. Certainly, OSA should be considered and treated if any symptoms are present. Typical hypnotic medications for insomnia may increase the risk of falls and injuries and should be used judiciously. Trazodone at low doses may improve total sleep time; otherwise, medications (including melatonin) and light therapy have not been shown to be effective in AD.<sup>24,25</sup> Behavioral and pharmacologic treatments for sleep-wake disorders in dementia are under active investigation.

## SLEEP-WAKE DISORDERS IN PARKINSON DISEASE

PD is the second most common neurodegenerative disorder. Disorders of sleep and alertness affect most patients throughout the course of PD. Despite this, sleep disorders remain underreported by patients and underrecognized by health care professionals. All categories of sleep disorders are associated with PD, and many have unique aspects when present in PD that likely reflect the interaction of PD-specific neurodegeneration with mechanisms regulating sleep and alertness.<sup>26</sup>

### Insomnia

Insomnia is the most common sleep disorder in PD. Sleep maintenance insomnia, frequently referred to as

sleep fragmentation, is the most common type of insomnia in PD. Up to 80% of patients report sleep fragmentation and early morning awakenings. The etiology of sleep fragmentation in PD encompasses the overnight emergence of motor PD symptoms, effects of dopaminergic medications on sleep, coexistence of other primary sleep and psychiatric disorders, autonomic dysfunction, and the influence of the primary neurodegenerative process on sleep-wake regulatory centers (Case 10-2).<sup>27</sup>

Two scales have been developed to assess sleep problems in PD, namely the Parkinson Disease Sleep Scale and the Scales for Outcomes in PD Sleep Scale (SCOPA-S) scale.<sup>28</sup> These scales complement the clinical sleep history,

### KEY POINTS

- Sleep disorders affect the majority of patients with Parkinson disease. Sleep dysfunction in Parkinson disease is underdiagnosed by health professionals and underreported by patients.
- Sleep fragmentation is the most common sleep disturbance in Parkinson disease.
- The Parkinson Disease Sleep Scale and the Scales for Outcomes in Parkinson Disease Sleep Scale are specific to Parkinson disease and are useful in assessing sleep in patients with the disease.

## Case 10-2

A 69-year-old man presented with his wife for follow-up of his Parkinson disease (PD). His daytime motor symptoms of PD were well managed with carbidopa/levodopa 25 mg/100 mg 2 tablets 3 times a day and amantadine 100 mg 3 times a day. He endorsed prominent fatigue. Since his last office visit, his wife found him more withdrawn and unhappy. He also reported difficulties with sleep. He fell asleep without problems, but kept waking up every 2 hours thereafter. Sometimes, this was caused by a need to urinate, which had increased over the past 6 to 9 months. He also endorsed difficulties with turning in bed because of overnight stiffness. Since the last office visit, he had begun to wake up at 4:30 AM and was unable to fall back to sleep.

**Comment.** Insomnia is common in PD. This patient had fragmented sleep and early morning awakenings. The case illustrates the multifactorial etiology of insomnia associated with PD. It appeared that this patient had developed a depressed mood since the last office visit. He also had an emergence of overnight motor symptoms of PD along with manifestations of autonomic dysfunction (nocturia), both of which can exacerbate poor sleep. Finally, he took amantadine at bedtime, which may have caused fragmented sleep because of its alerting properties. Treatment of depression along with the addition of long-acting carbidopa/levodopa at bedtime may improve mood and control overnight PD symptoms, which will likely improve sleep. A consultation with a urologist and subsequent treatment with a urodynamic agent may improve nocturia and reduce overnight awakenings. Finally, moving the bedtime dose of amantadine earlier in the day may improve sleep continuity. The possibility of comorbid sleep apnea and need for polysomnography may also be considered in this case, since untreated sleep-disordered breathing may occasionally present with sleep maintenance insomnia and excessive arousal, rather than predominant daytime sleepiness or symptoms of disruptive snoring.

## KEY POINTS

- Dopaminergic medications frequently cause excessive daytime sleepiness, where the major predictive factor for excessive daytime sleepiness is not the specific type of dopaminergic agent, but rather the total dose of dopaminergic therapy.
- Excessive daytime sleepiness and sleep attacks pose significant safety issues for patients with Parkinson disease. Patients who experience sleep attacks should be advised not to drive until the issue is resolved.

which should emphasize factors specific to PD. A thorough review of the medication regimen is needed. Optimization of overnight PD symptoms, frequently with extended release levodopa, may be beneficial for sleep. Management of urinary dysfunction or nocturia with urodynamic agents should be considered. Overnight hallucinations and confusion, especially in patients with PD with cognitive impairment, should not be overlooked, as they pose significant challenges to overnight sleep.

Treatment of insomnia associated with PD encompasses behavioral and pharmacologic interventions. Proper sleep hygiene should be implemented. Classic behavioral approaches such as stimulus control and sleep restriction have not been studied in PD, but certainly should be considered in management.

## Sleep-Disordered Breathing

Sleep-disordered breathing has not been extensively studied in the PD population. Initial reports of irregular respiratory patterns with nocturnal worsening and central hypoventilation come from patients with postencephalitic parkinsonism. Although sleep-disordered breathing remains common in PD, there is a similar prevalence of sleep-disordered breathing in PD compared with the general population.<sup>29,30</sup>

While OSA is the most common type of sleep-disordered breathing in the general population, obstructive, central, and mixed apneas may be equally represented in PD. Obesity, a strong predictor of sleep-disordered breathing in the general population, is not predictive of this disorder in PD, since most patients with PD with sleep-disordered breathing have normal body mass indices. No clear relationship exists between the prevalence of sleep-disordered breathing

and PD duration or medication regimen. Sleep-disordered breathing does not correlate well with self-reported and objective measures of sleepiness in PD. The severity of sleep-disordered breathing and mean overnight oxygen saturation levels correlate with PD severity.

Nasal positive airway pressure (nPAP) remains the main treatment of sleep-disordered breathing in PD. Adaptive servo-ventilation may be the preferred type of positive airway pressure (PAP) in patients with PD with predominant central apneas. Selection of an appropriate nPAP mask is very important as it may determine the success of nPAP. In cases where nPAP is not tolerated, non-PAP treatment modalities, such as a fitted dental oral appliance or surgical interventions, may be considered. Improvements in overnight chest wall rigidity with modification of PD regimen may also improve respiratory function and sleep-disordered breathing.

## Excessive Daytime Sleepiness

Excessive daytime sleepiness affects up to 50% of patients with PD.<sup>31</sup> Male gender, duration, and severity of PD have been associated with excessive daytime sleepiness. Excessive daytime sleepiness in PD has been associated with the unexpected sudden onset of sleep, or “sleep attacks,” that pose important safety implications, as episodes of falling asleep at the wheel have been reported in up to 23% of patients with PD.<sup>32</sup> The etiology of excessive daytime sleepiness encompasses the primary neurodegenerative process, complex medication regimens, age-related changes in the sleep architecture, and coexistent sleep disturbances. The loss of hypocretin/orexin has been reported in PD and is likely an important culprit of excessive daytime sleepiness.<sup>33</sup> Dopaminergic medications frequently cause excessive daytime sleepiness, where

the major predictive factor for excessive daytime sleepiness is not the specific type of dopaminergic agent, but rather the total dose of dopaminergic therapy.

Treatment of excessive daytime sleepiness in patients with PD is challenging. Patient education about healthy sleep hygiene and timely diagnosis of a coexistent sleep disorder is essential. Somnifac medications should be minimized, and those with activating properties (eg, selegiline or amantadine) should be given earlier in the day. The dose of dopaminergic medications may need to be reduced. Patients who experience sleep attacks should be advised not to drive until the issue is resolved. Stimulants have been used for the treatment of excessive daytime sleepiness with variable success, and because of their adverse effects, are rarely used in PD. Modafinil has been evaluated for the treatment of excessive daytime sleepiness in PD, and while some trials demonstrated improvement in excessive daytime sleepiness with 100 mg/d to 200 mg/d, others did not find any benefit. Melatonin may be beneficial in improving sleep quality and reducing excessive daytime sleepiness in PD.

### Rapid Eye Movement Sleep Behavior Disorder

REM sleep behavior disorder (RBD) frequently precedes the onset of cardinal diagnostic features of PD and other  $\alpha$ -synucleinopathies. (For more information on RBD, refer to the article “Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias” by Birgit Högl, MD, and Alex Iranzo, MD,<sup>34</sup> in this issue of *Continuum*.) RBD is present in approximately one-third to one-half of patients with PD and is more prevalent among patients with an akinetic/rigid phenotype and

in patients who experience falls, higher disease severity, greater motor fluctuations, and an increased levodopa dose.<sup>35</sup> The presence of RBD predicts greater cognitive decline in PD. Prospective studies have revealed phenoconversion rates of idiopathic RBD to PD in approximately 75% to 90% of patients 10 to 14 years following RBD diagnosis.<sup>36–38</sup> The most commonly used medications to control RBD attacks are melatonin and clonazepam. Melatonin should be the first-line therapy in patients with PD who have RBD since it has fewer sedating properties compared with clonazepam.

### Restless Legs Syndrome

For a full discussion concerning the diagnosis and treatment of restless legs syndrome (RLS), refer to the article “Restless Legs Syndrome and Sleep-Related Movement Disorders” by Lynn Marie Trotti, MD, MSc,<sup>39</sup> in this issue of *Continuum*. RLS appears to be more common in PD than in the general population and affects approximately 20% of patients with PD. Greater severity of PD, coexistent depression, and reduced serum iron binding capacity are risk factors for RLS in PD. Although both PD and RLS respond favorably to dopaminergic medications, no pathologic similarities exist between these two disorders.

Diagnosis of RLS in PD may be challenging since several symptoms of PD, such as akathisia, overnight motor symptoms, and dystonic symptoms, may mimic RLS.<sup>40</sup> Furthermore, RLS may fluctuate similarly to PD symptoms, and both disorders are treated with similar medications. The most commonly used medications for the treatment of RLS are dopamine agonists, anticonvulsants, clonazepam, and opioids. Levodopa for RLS treatment in patients with PD should be avoided because of risks of rebound

#### KEY POINTS

- Rapid eye movement sleep behavior disorder frequently precedes the onset of cardinal diagnostic features of Parkinson disease and other  $\alpha$ -synucleinopathies.
- Rapid eye movement sleep behavior disorder is present in approximately one-third to one-half of patients with Parkinson disease and is more prevalent among patients with an akinetic/rigid phenotype and in patients who experience falls, higher disease severity, greater motor fluctuations, and an increased levodopa dose.
- Prospective studies have revealed phenoconversion rates of idiopathic rapid eye movement sleep behavior disorder to Parkinson disease in approximately 75% to 90% of patients 10 to 14 years following diagnosis of rapid eye movement sleep behavior disorder.
- Restless legs syndrome appears to be more common in Parkinson disease than in the general population and affects approximately 20% of patients with Parkinson disease. Greater severity of Parkinson disease, coexistent depression, and reduced serum iron binding capacity are risk factors for restless legs syndrome in Parkinson disease.



and augmentation, although most patients with PD will continue to require usual doses of levodopa for their motor symptom management. Iron supplementation should be considered if ferritin levels are low. Medications known to exacerbate RLS such as dopamine blockers and anticholinergic and antihistaminic agents should be discontinued if possible.

### **SLEEP COMORBIDITIES IN AMYOTROPHIC LATERAL SCLEROSIS AND NEUROMUSCULAR DISORDERS**

The wide variety of neuromuscular disorders associated with various sleep

disorders, most commonly hypoventilation due to restrictive thoracic disease from weakness of respiratory musculature, are reviewed in **Table 10-3**.<sup>41</sup> A common and illustrative disease is ALS, which is an incurable disease characterized by progressive degeneration of the upper and lower motor neurons. Survival is approximately 3 to 5 years, with death usually due to respiratory failure. Lying flat places the diaphragm at a mechanical disadvantage, so hypoventilation due to restrictive thoracic disease in ALS often presents as orthopnea at night, prior to daytime respiratory symptoms. Morning headaches, daytime sleepiness, and

**TABLE 10-3 Sleep Disorders in Neuromuscular Diseases**

Neuromuscular Disorder	Common Sleep Comorbidities	Notes
Amyotrophic lateral sclerosis	Hypoventilation, obstructive sleep apnea	Noninvasive ventilation improves survival and quality of life
Duchenne muscular dystrophy	Hypoventilation	Both fixed restrictive and functional restrictive defects, often require tracheostomy because of 24 hour/d ventilation
Myotonic dystrophy	Obstructive sleep apnea, central sleep apnea, hypersomnia	Frequent central apneas in response to positive airway pressure treatment, low hypocretin/orexin levels in CSF
Inflammatory myopathies	Obstructive sleep apnea, hypoventilation	Frequently asymptomatic, so screening is essential; dermatomyositis most commonly affected; hypoventilation is related to diaphragmatic weakness
Myasthenia gravis	Obstructive sleep apnea	Consider nasal continuous positive airway pressure therapy, alternative measures (position restriction, dental appliance, nasal expiratory positive airway pressure device)
	Restless legs syndrome	Consider iron replacement therapy; dopamine agonist, gabapentin, enacarbil, or pregabalin
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	Hypoventilation, rapid eye movement (REM) sleep behavior disorder	May require intubation in acute phase; REM sleep behavior disorder and other narcolepsylike symptoms may be related to low orexin levels in CSF
Charcot-Marie-Tooth disease	Restless legs syndrome	Treatment strategy same as idiopathic restless legs syndrome

CSF = cerebrospinal fluid.

cognitive dysfunction are also common symptoms of hypoventilation. Furthermore, because of weakness of oropharyngeal musculature, patients with ALS are at high risk of OSA, thus snoring, witnessed apneas, or frequent nocturnal arousals may be presenting symptoms. Other factors contribute to poor sleep in ALS, such as central apneas, restless legs syndrome, muscle cramps, discomfort from immobility, depression, and ALS-associated dementia. Therefore, evaluation for hypoventilation and sleep disorders should be part of comprehensive ALS care.

Screening for hypoventilation is frequently done in the clinic via spirometry, specifically using the forced vital capacity. However, forced vital capacity measured in the upright position is not particularly sensitive, so measurement in both supine and upright positions may demonstrate decline with recumbency. Nocturnal desaturations with SaO<sub>2</sub> of less than 90% for 1 or more cumulative minutes are more sensitive than forced vital capacity for detecting hypoventilation; however, pulse oximetry may miss mild hypoventilation.<sup>42</sup> Furthermore, adding supplemental oxygen to treat hypoxia in patients with neuromuscular bellows failure is contraindicated, since this may cause additional carbon dioxide retention and lead to worsening of symptoms or even acute respiratory failure, as illustrated in **Case 10-3**. Rather, a full assessment for hypoventilation should include spirometry in the erect and supine positions, lung volumes, maximal inspiratory and expiratory pressures (peak inspiratory/ expiratory forces), sniff nasal pressure, and arterial blood gases.<sup>35</sup> Polysomnography, ideally with transcutaneous Pco<sub>2</sub> monitoring, may be indicated for identifying sleep-related hypoventilation (in which Pco<sub>2</sub> increases more than 10 mm Hg during sleep) and OSA.

The most effective treatment for sleep-related hypoventilation in ALS is nocturnal ventilation. Both invasive (via tracheostomy) and noninvasive ventilation (NIV) are available. NIV has been shown to prolong survival by approximately 7 to 12 months,<sup>43</sup> longer than the benefit from riluzole. NIV extends quality of life for both patient and caregiver and slows respiratory decline.<sup>43,44</sup> The exception is bulbar-predominant ALS, in which no study has identified a survival benefit from NIV; yet, NIV improves sleep quality in bulbar-predominant ALS.<sup>43</sup> Therefore, NIV should be offered, unless patients prefer invasive ventilation, “at the earliest sign of nocturnal hypoventilation or respiratory insufficiency,” according to the AAN practice parameters.<sup>42</sup>

NIV is a subset of PAP, and the “target” of PAP therapy can be pressure or volume. Until recently, bilevel PAP was commonly used for NIV. However, in cases of increased resistance to air entry due to secretions or edema during infection, bilevel PAP will deliver a lower volume at the time patients most need ventilatory support. Therefore, volume-targeted ventilation modes are preferred in ALS, in which respiratory infection risk is high. Previously, volume-targeted NIV required nonvented masks, which greatly limited the selection of masks. Recently, volume-assured pressure support has been introduced for use with vented masks, allowing for a greater variety of masks to be used with NIV. In volume-assured pressure support, a volume target is set, along with a range of pressures that the machine is permitted to use to reach the set target; this theoretically allows the lowest required pressure to be used, possibly improving comfort and compliance, although prospective studies demonstrating therapeutic

## KEY POINTS

- Pulse oximetry is incompletely sensitive for hypoventilation, and supplemental oxygen alone is contraindicated in patients with amyotrophic lateral sclerosis and neuromuscular bellows failure, since oxygen may worsen carbon dioxide retention and lead to acute respiratory failure.
- In addition to nocturnal pulse oximetry, erect and supine spirometry, maximal inspiratory/ expiratory force, sniff nasal pressure, and arterial blood gases should be obtained to assess for suspected hypoventilation in amyotrophic lateral sclerosis and other neuromuscular diseases.
- Noninvasive ventilation prolongs survival and maintains quality of life in patients with amyotrophic lateral sclerosis. Ventilation usually starts with nocturnal treatment and then expands to daytime treatment as symptoms progress.

### Case 10-3

A 75-year-old man presented with a 2-year history of frequent falls and clumsiness. He was diagnosed with amyotrophic lateral sclerosis and treated with 3 L/min oxygen based on hypoxemia on home oximetry. He was referred to sleep medicine for excessive daytime sleepiness. Sleep history revealed no snoring or witnessed apneas. He went to bed at 9:30 PM and woke frequently all night for no apparent reason. He used three pillows because of orthopnea, yet awakened with a headache daily at 7:00 AM. His wife described him sleeping “all day” for 1 to 2 hours at a time in a recliner; even when awake, he was unable to hold a conversation. His score on the Epworth Sleepiness Scale was elevated at 14 out of 24. Pulmonary function testing revealed a restrictive defect with forced vital capacity of 58% predicted, and arterial blood gas on room air showed severe hypercapnia with pH 7.40,  $P_{CO_2}$  67 mm Hg, and  $P_{O_2}$  59 mm Hg. Polysomnography demonstrated severe obstructive sleep apnea with an apnea-hypopnea index of 38 events per hour of sleep. Sleep-related hypoventilation was demonstrated through an elevation of  $P_{CO_2}$  from 74 mm Hg to 85 mm Hg during sleep. The patient was titrated with volume-assured pressure support. At optimal settings, the patient’s obstructive sleep apnea was fully treated,  $P_{CO_2}$  improved to 59 mm Hg, and there was no oxygen requirement. He was set up for nocturnal volume-assured pressure support at home with a full face mask. At follow-up 2 months later, his wife described him as “back to himself,” alert, and witty. He was able to sleep soundly all night with one pillow, and he awakened feeling refreshed without a headache. He no longer took any naps, and his score of the Epworth Sleepiness Scale normalized to 0 out of 24.

**Comment.** This case illustrates the importance of treating underlying hypoventilation rather than merely treating hypoxemia with supplemental oxygen, which can worsen carbon dioxide retention and subsequent drowsiness and headaches. Additionally, obstructive sleep apnea may be present even in the absence of obvious symptoms in amyotrophic lateral sclerosis, and noninvasive ventilation should be titrated to treat obstructive sleep apnea in addition to providing ventilatory support.

equivalency and tolerability to bilevel PAP (BiPAP) are needed.

OSA is quite common in ALS. Standard NIV settings (tidal volume is determined by height) may be insufficient to maintain a patent upper airway in comorbid OSA. A recent study found that untreated obstructive events shortened survival in ALS despite treatment with standard NIV, and these obstructive events were not detected by pulse oximetry.<sup>45</sup> Therefore, in comorbid OSA, polysomnography for NIV titration is recommended to identify settings optimal for treating hypoventilation and OSA. Polysomnography

also offers a good opportunity to test different mask models, since mask fit is exceptionally important for patients with ALS who may ultimately need to use NIV masks 24 hours per day.

Initially, most patients with ALS require NIV only when sleeping. However, as ALS progresses, dyspnea, accessory muscle use, or hypercapnia/hypoxemia will eventually also occur during the daytime. Mouthpiece ventilation is useful for bridging patients between nocturnal and around-the-clock ventilation. With this mode, the patient can “suck” on a strawlike or similar mouthpiece interface for

ventilation as needed. Eventually, patients with ALS will require 24-hour ventilator support. Whether the ventilator support modality is noninvasive or invasive, patients and caregivers should be counseled well in advance of the progressive decline in respiratory function. As respiratory insufficiency progresses, an accompanying issue is the inability to clear secretions from the upper airway, so prescription of cough assist and suctioning devices should also be considered in parallel to optimizing NIV PAP therapy to ensure tolerability and adequate ventilatory support.

## CONCLUSION

Essentially all classes of neurologic diseases are associated with one or more sleep disorders. Identifying and treating sleep dysfunction can help patients remarkably in terms of their sleep-related symptoms and quality of life and may also have a beneficial effect on the underlying neurologic disease symptom severity. Assessment for sleep disturbances should be routine in the care of patients with neurologic diseases.

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# Sleep-Wake Disorders of Childhood

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## ABSTRACT

**Purpose of Review:** Sleep-wake disorders occur in 10% to 28% of children and differ somewhat in pathophysiology and management from sleep-wake disorders in adults. This article discusses the diagnosis and management of key childhood sleep disorders.

**Recent Findings:** The role of sleep in memory consolidation and in the facilitation of learning has been increasingly recognized, even at the toddler stage. Cataplexy, a key feature of narcolepsy type 1, may be subtle in childhood and characterized by transient muscle weakness isolated to the face. Children with obstructive sleep apnea and restless legs syndrome display prominent neurobehavioral symptoms such as daytime inattentiveness and hyperactivity, so it is important to elicit a sleep history when these symptoms are encountered. Systemic iron deficiency occurs in about two-thirds of children with restless legs syndrome and is easily treatable. Parasomnias arising out of non-rapid eye movement (REM) sleep, such as confusional arousals and sleepwalking, may be difficult to distinguish from nocturnal seizures, and, in many cases, video-EEG polysomnography is required to differentiate between causes.

**Summary:** Clinicians should routinely integrate the assessment of sleep-wake function into their practices of neurology and child neurology because of the opportunity to improve the quality of life of their patients.

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## INTRODUCTION

Pediatric sleep-wake disorders are very common. A prospective study followed 359 mother-child pairs from the birth of the child until 36 months of age and administered surveys about the child's sleep at 6, 12, 24, and 36 months of age; the findings showed that the prevalence of sleep disorders at each assessment point was 10%.<sup>1</sup> Another large study found that 28% of children aged 11 to 15 years had sleep disturbances such as insomnia, snoring, or parasomnias.<sup>2</sup> Childhood sleep-wake disorders can contribute significantly to behavioral dysregulation and impairment of cognition and learning and differ from sleep problems in adults because of the continuous neurodevelopmental changes that are evolving from infancy through

adolescence. This article highlights key issues of pediatric sleep medicine that are relevant to both child and adult neurologists.

## SLEEP ONTOGENY

Developmental aspects of sleep regulation help us understand the pathophysiologic aspects of childhood sleep disorders. The overall quantity of sleep over a 24-hour period and the temporal organization of various sleep stages evolves continuously from infancy through adolescence. Wakefulness can be differentiated from sleep by 27 to 28 weeks postconceptional age in the preterm infant on the basis of clinical observation and EEG patterns. At this age, about 80% of total sleep time is active (rapid eye movement [REM]) sleep, characterized by an

irregular respiratory pattern, intermittent electromyographic activity, and low-voltage mixed-frequency EEG activity. By full term (40 weeks post-conceptional age), active (REM) sleep decreases to about 50% of the total sleep time, with a corresponding increase in the proportion of quiet (non-REM) sleep. Sleep spindles and K complexes, which reflect maturation of thalamocortical activity, appear by 2 to 3 months of age in full-term infants. By 4 to 6 months of age after term, non-REM sleep becomes further differentiated into N1, N2, and N3 sleep stages, which have progressively lighter to deeper arousal thresholds, respectively.

Sleep stage N3 is characterized by generalized slow-wave activity in the 0.5 Hz to 4 Hz range on EEG. N3 (slow-wave) sleep occurs predominantly in the first third of the night. Children experience large amounts of N3 sleep, which is linked to the release of growth hormone and the consolidation of explicit memories. REM sleep decreases progressively from the newborn period through ages 3 to 4 years so that by the age of 3 years, it constitutes only about 20% to 25% of total sleep.

The role of sleep in child development is underscored by the fact that short-term memories stored in the hippocampus become consolidated into long-term memories in the neocortex during the N3 sleep stage, at which time a replay of short-term memory events occurs. At the electrophysiologic level, this correlates with hippocampal field potential oscillations of approximately 180 Hz, which are termed *ripples*.<sup>3,4</sup> Sleep spindles, volleys of thalamocortical impulses, also play a role in sleep-dependent learning. Both spindles and ripples are, in turn, modulated by cortical slow waves of approximately 1 Hz. An example of the role sleep has in mem-

ory formation is that 15-month-old toddlers assimilate new linguistic information better if allowed to take a nap within 4 hours of presentation of the stimulus, as compared to continued wakefulness without an ensuing nap.<sup>5</sup>

### Shifts in Temporal Organization of Sleep Architecture and Time of Sleep Onset

Prior to the age of 3 months, infants transition from wakefulness directly into REM sleep. After this age, however, children tend to shift from wakefulness into non-REM sleep, with REM sleep occurring 90 to 140 minutes after initial sleep onset. Elementary school-age children usually become sleepy around 8:00 PM to 8:30 PM. During the transition from prepuberty to puberty, a shift occurs, and melatonin is released at a later time, with a corresponding delay in the sleep-onset time to 10:30 PM or 11:00 PM, which also correspondingly leads to a later shift in the morning wake-up time. Also, melatonin secretion declines with advancing Tanner stage during sexual development,<sup>6</sup> more so in boys than girls. When juxtaposed with early high school start times of around 7:30 AM, it is easy to understand why most teenagers are chronically sleep deprived.

### How Much Sleep Do Children Need?

Expert consensus opinions exist regarding the amount of sleep children need, but there are insufficient recommendations based on hard data. The widely cited opinion of the National Sleep Foundation,<sup>7</sup> shown in **Table 11-1**, provides an approximation of the optimum amount of sleep needed. More recently, a panel of experts convened by the American Academy of Sleep Medicine also came to approximately the same conclusions concerning

#### KEY POINTS

- The overall quantity of sleep over a 24-hour period and the temporal organization of various sleep stages evolves continuously from infancy through adolescence.
- Children experience large amounts of the N3 sleep stage, which is linked to the release of growth hormone and the consolidation of explicit memories.
- During transition from prepuberty to puberty, a shift occurs, and melatonin is released at a later time, with a corresponding delay in sleep-onset time to 10:30 PM or 11:00 PM.

**KEY POINT**

- Inadequate sleep hygiene has become the foremost etiology for daytime sleepiness in adolescents.

**TABLE 11-1** Approximate Sleep Requirements at Various Ages<sup>a</sup>

Age	Hours of Sleep
Newborns, 0–2 months	12–18 hours
Infants, 3–11 months	14–15 hours
Toddlers, 12–36 months	12–14 hours
Preschoolers, 3–5 years	11–13 hours
School-age children, 5–10 years	10–11 hours
Teenagers, 10–17 years	8–9.25 hours

<sup>a</sup> Data from National Sleep Foundation.<sup>7</sup>  
[nationalsleepfoundation.org/article/sleep](http://nationalsleepfoundation.org/article/sleep).

hours of sleep needed. This was based upon a review of 864 published articles addressing childhood sleep duration. Sleeping the recommended hours was associated with improved health outcomes, including better attention, behavior, learning, memory, emotional regulation, quality of life, and physical and mental health.<sup>8</sup>

Sleep needs are most likely influenced by highly individualized determinants, including genetic polymorphisms in *PER* and adenosine receptor genes involved in sleep homeostasis and circadian regulation, as well as differing optimal sleep needs for cardiometabolic health, mood regulation, memory consolidation, and learning. Furthermore, the restorative function of sleep may be related both to sleep quantity and circadian factors (ie, when, over a 24-hour period, we tend to sleep or stay awake).

**CLINICAL ASSESSMENT**

The sleep history should inquire into the sleep environment (eg, child's own bed or parents' bed), bedtime,

approximate sleep-onset time, sensation of discomfort in the extremities (restless legs syndrome [RLS]), intrusive thoughts or worries (anxiety), habitual snoring, periods of observed apnea and restless sleep (obstructive sleep apnea [OSA]), unusual nighttime events such as sleepwalking or confusion (parasomnias), daytime sleepiness (hypersomnia disorders), mood disturbances, and medications.

The sleep-related examination should include assessment for height, weight, body mass index, presence of craniofacial anomalies, tonsillar hypertrophy and whether the oral airway is crowded, examination of the anterior nasal passages, and auscultation of the heart and lungs.

**EXCESSIVE DAYTIME SLEEPINESS**

Excessive daytime sleepiness in childhood is a frequently overlooked, although common and disabling, symptom. The prevalence of excessive daytime sleepiness in childhood has been established based on questionnaire studies. Worldwide, the prevalence of excessive daytime sleepiness in childhood and adolescence is estimated at 4% to 20%.<sup>9,10</sup> A detailed sleep-wake history may help determine a specific etiology and formulation of a management plan. **Table 11-2** lists some of the common childhood disorders leading to excessive daytime sleepiness. Only some of the prototypical disorders leading to excessive daytime sleepiness are discussed in this section.

**Inadequate Sleep Hygiene**

Inadequate sleep hygiene has become the foremost etiology for daytime sleepiness in adolescents. It is driven by several factors including nocturnal mentally activating habits before or during usual expected bedtime hours, such as watching television in the 1 to 2 hours prior to bedtime; playing with

**TABLE 11-2** Causes of Excessive Daytime Sleepiness in Childhood and Adolescence

- ▶ **Circadian Rhythm Sleep-Wake Disorders**
  - Delayed sleep-wake phase disorder
  - Irregular sleep-wake rhythms
  - Non-24-hour sleep cycles
- ▶ **Environmental**
  - Illicit substances
  - Inadequate sleep hygiene
  - Over-the-counter medicines (eg, diphenhydramine)
  - Prescription medicines
- ▶ **Primary Disorders of Vigilance**
  - Idiopathic hypersomnia
  - Kleine-Levin syndrome (periodic hypersomnia)
  - Narcolepsy with cataplexy (type 1)
  - Narcolepsy without cataplexy (type 2)
  - Secondary narcolepsy (eg, posttraumatic or postencephalitic)
- ▶ **Psychiatric**
  - Depression
- ▶ **Respiratory**
  - Obstructive hypoventilation
  - Obstructive sleep apnea

electronic devices or cell phones; caffeine, tobacco, or illicit substance use at night; taking a warm shower or exercising close to bedtime; and eating or drinking in the middle of the night. The sleep history should determine details regarding the sleep period, including what time the patient goes to bed and when sleep onset occurs for both school nights and non-school nights. The physician

must also be alert toward the possibility of illicit substance use and drug-seeking behaviors, such as requesting stimulant medications by fabricating a history of sleepiness. Taking afternoon naps in adolescence can also diminish the drive to fall asleep at night. The use of electronic devices is also a very common contributing problem.

The management for inadequate sleep hygiene consists of identifying the offending stimulus via the sleep history and educating the patient and his or her parents toward corrective behaviors. Urine toxicology screens are indicated when drug diversion or abuse is suspected. Both the patient and parents need to be counseled about healthy sleep habits. Mid- to late-afternoon exercise, as tolerated, may facilitate restful sleep at night.

### Kleine-Levin Syndrome

Also referred to as recurrent or periodic hypersomnia, Kleine-Levin syndrome is encountered in adolescents and is about 4 times more common in adolescent males than females. The salient features of Kleine-Levin syndrome include periods of hypersomnia, inertia, and feelings of depersonalization. Hyperphagia and hypersexual behavior have been overemphasized and occur only in about 50% of patients. Periods of extreme sleepiness occur, lasting 14 to 18 hours per day for 1 to 2 weeks and, in about one-half of cases, may be associated with hyperphagia, anorexia, or hypersexual behavior. Feelings of depersonalization, amnesia, and cognitive difficulties may also occur.<sup>11</sup> In between these episodes, the patients are completely normal. Several of these episodes may occur per year. Intercurrent viral infections may trigger a sleepiness episode, but not on a consistent basis. No genetic predisposing factors exist. Prior neurologic and psychiatric history is also

### KEY POINTS

- The sleep history should determine details regarding the sleep period, including bedtime and when sleep onset occurs for both school and non-school nights.
- The use of electronic devices is a very common contributing problem to inadequate sleep hygiene.
- The salient features of Kleine-Levin syndrome include periods of hypersomnia, inertia, and feelings of depersonalization. Hyperphagia and hypersexual behavior occur only in about 50% of patients.
- In Kleine-Levin syndrome, intercurrent viral infections may trigger a sleepiness episode, but not on a consistent basis.



**KEY POINT**

- About one-third of patients with narcolepsy experience the onset of symptoms in the first or second decade of childhood.

unremarkable. School attendance and the overall quality of life may be considerably impacted. No specific abnormalities are seen on neuroimaging tests or routine testing of the CSF. Nocturnal polysomnography obtained during the first 2 to 3 days of sleepiness may show increased arousals, decreased sleep efficiency, and suppression in the proportion of time spent in N3 sleep. These findings may resolve in the latter half of the sleepy period. During relapses, the CSF hypocretin/orexin levels may be reduced in comparison to periods of remission, but the magnitude of decreased CSF hypocretin is mild when compared to patients with narcolepsy-cataplexy.<sup>12</sup> Empiric evidence suggests that lamotrigine and lithium are modestly effective in preventing relapses or decreasing the duration of sleepy periods in patients with Kleine-Levin syndrome. In a recent open-label, controlled study, the risk-benefit ratio of lithium was superior to no therapy, presumably on account of anti-inflammatory or neuroprotective effects.<sup>13</sup> In general, Kleine-Levin syndrome episodes become gradually less frequent over time and gradually spontaneously resolve.

**Narcolepsy**

Narcolepsy is a prototypic disorder of excessive sleepiness that occurs in both adults and children, with about one-third of patients having onset of symptoms during the first or second decade. Narcolepsy is characterized by an overwhelming sleepiness, variable presence of sudden muscle weakness provoked by emotional stimuli, fright, or the anticipation of a reward (cataplexy), vivid dreams at sleep onset (hypnagogic hallucinations), transient inability to move as the patient drifts off to sleep or wakes from sleep (sleep paralysis), and instability of nocturnal

sleep with heightened arousals. Based upon the presence or absence of cataplexy, the *International Classification of Sleep Disorders, Third Edition (ICSD-3)* categorizes the disorder into type 1 and type 2, respectively.<sup>14</sup> Type 1 is more common in childhood as compared to type 2. Narcolepsy type 1 may have an onset anywhere between 3 and 17 years of age.

Familial clustering of narcolepsy is recognized, as the risk of developing narcolepsy is 1% to 2% for first-degree relatives of patients with narcolepsy (20-fold to 40-fold higher risk than in the general population).<sup>15</sup> The haplotype human leukocyte antigen DQB1\*0602 is present in more than 95% of narcolepsy type 1 cases, as compared to a 25% to 30% prevalence in the general population, and may predispose patients to narcolepsy with cataplexy following likely triggers such as infections (commonly mycoplasma, Epstein-Barr virus, influenza, or streptococcus) or immunizations. Through mechanisms that are not yet fully defined, there is likely to be activation of an immune-mediated disturbance that leads to near-complete loss of dorsolateral hypothalamic hypocretin-secreting neurons.<sup>16</sup> Hypocretinergic neurons project widely to the ventral forebrain to enhance alertness and also to areas of the brainstem to modulate monoamine release and motor control. The loss of hypocretin leads to hypersomnia, cataplexy, and unstable nocturnal sleep (with or without periodic limb movements [PLMs] of sleep). Patients with narcolepsy type 2 lack cataplexy and may manifest hypersomnia, sleep paralysis, and hypnagogic hallucinations. Some individuals with narcolepsy type 2 may develop cataplexy several years later, thus evolving into narcolepsy type 1, while others may have narcolepsy type 2 throughout their lives.

The most disabling clinical manifestation of childhood narcolepsy is profound daytime sleepiness. Despite having slept through the night, the patient may fall asleep involuntarily on multiple occasions during the day (while sitting at a desk, during conversations, and even while eating). An increase in the total sleep time over the 24-hour period occurs around the time of symptom onset and gradually reduces over months.<sup>17</sup> The Epworth Sleepiness Scale for Children and Adolescents or the Pediatric Daytime Sleepiness Scale can be used to assess the degree of sleepiness. Sleepiness may be associated with mood swings, inattentiveness, and problems with memory and learning. Anxiety and feelings of sadness may impair social interactions. Children younger than ages 8 to 10 years may show subtle cataplexy in the form of transient jaw weakness or head rolling; laughter may not be a consistent trigger for cataplexy in preschool-age children. Patients do not consistently report cataplexy; hence, the clinician may need to probe with leading questions concerning weakness provoked by emotions, characteristically by laughter. When severe, cataplexy can lead to falls or the legs feeling weak or rubbery; when subtle, however, it may manifest itself only with momentary masseter muscle weakness with the jaw dropping open or a slight head and neck roll.<sup>17</sup> Precocious puberty and obesity are other common features at the onset of narcolepsy type 1.<sup>18</sup> Sleep at night may be disrupted by PLMs or REM sleep behavior disorder.

**Diagnosis.** The diagnosis of narcolepsy is generally established using nocturnal polysomnography (sleep-onset REM period, fragmented sleep, and REM sleep without atonia are common findings), followed the next day by the multiple sleep latency test

(MSLT). On the MSLT, the clinician is likely to find a decreased sleep latency of fewer than 8 minutes and two or more sleep-onset REM periods.<sup>19</sup> If the nocturnal polysomnogram has a sleep-onset REM period, the clinician needs to see only one additional sleep-onset REM period on the MSLT to establish the diagnosis. Reference values for the MSLT in children are slightly higher than those of adults. A urine drug screen should be obtained routinely when the mean sleep latency is fewer than 8 minutes. Caveats about sleep laboratory evaluations are that testing is valid only in children older than 5 years of age, and that patients must be drug free in the preceding 2 to 3 weeks prior to testing to avoid confounding the results or masking diagnostic sleep-onset REM periods by stimulants or antidepressants that suppress and delay entry into REM sleep. CSF may show absent to very low levels of hypocretin-1 (less than 110 pg/dL) in patients with narcolepsy-cataplexy.<sup>20</sup> Hypocretin analysis has limited clinical availability in the United States, but is helpful in enabling diagnosis of narcolepsy type 1 when polysomnography and MSLT are not applicable (eg, in patients younger than 5 years of age) or when the patient is receiving a REM-suppressant agent such as a selective serotonin reuptake inhibitor (SSRI) that cannot be safely stopped because of concerns about exacerbating comorbid depression.

The differential diagnosis of narcolepsy includes abnormal sleep hygiene with consequent insufficient sleep at night, drug-seeking behavior, depression, and circadian rhythm sleep-wake disorders such as delayed sleep-wake phase disorder. If a clinical suspicion of narcolepsy exists and sleep studies are equivocal, a serial battery of polysomnography and MSLT several months apart may be needed because

#### KEY POINTS

- Children with narcolepsy may show subtle cataplexy with transient jaw weakness or head rolling, and laughter may not be a consistent trigger in children.
- Precocious puberty and obesity are other common features accompanying the onset of narcolepsy type 1.

polysomnographic features of narcolepsy may evolve gradually over time. Secondary narcolepsy as a consequence of anatomic or metabolic brain lesions is rare, but can develop in patients with primary brain tumors such as craniopharyngioma, head injury, encephalitis, myotonic dystrophy type 1, and Niemann-Pick disease type C (a disorder of intracellular cholesterol transport).

**Management.** The first step in management is counseling. The patient and family should be informed that narcolepsy is a life-long disorder. The sleep-wake schedule should be regular, and planned naps of 20 to 30 minutes should be put in place at school or upon return home from school. Whenever possible, driving should be avoided, as should the use

of alcohol. Physical activity is a useful antidote to sleepiness; hence, the patient should exercise regularly. High school graduates may require counseling about the choice of a career and course load in college. Referral to patient and family support organizations such as the Narcolepsy Network ([narcolepsynetwork.org](http://narcolepsynetwork.org)) or Wake Up Narcolepsy ([wakeupnarcolepsy.org](http://wakeupnarcolepsy.org)) is also recommended.

Regarding pharmacotherapy of narcolepsy (**Table 11-3**), the clinician should initially target the symptom that is most bothersome to the patient. If sleepiness is the major concern, prescribing a formulation of methylphenidate or amphetamine or a wakefulness-promoting agent such as modafinil or armodafinil is recommended. Conversely, if cataplexy is more bothersome, sodium

**TABLE 11-3** Childhood Narcolepsy Pharmacotherapy

Symptom	Drug	Potential Side Effects
Daytime sleepiness	Methylphenidate	Loss of appetite, suppression of growth, exacerbation of anxiety, nervousness
	Dextroamphetamine, amphetamine-dextroamphetamine mixture	Loss of appetite, suppression of growth, exacerbation of anxiety, nervousness
	Modafinil, armodafinil	Headache, precipitation of Stevens-Johnson syndrome, decreases the potency of concurrently administered oral contraceptives
	Sodium oxybate	Tremor, constipation, bed-wetting, exacerbation of sleep apnea, weight loss, exacerbation of depression
Cataplexy	Sodium oxybate	Tremor, constipation, bed-wetting, exacerbation of sleep apnea, weight loss, exacerbation of depression
	Venlafaxine, protriptyline, clomipramine	Drowsiness, weight gain, tremor
	Fluoxetine, sertraline	Nervousness, insomnia, increased risk of suicidal thoughts
Periodic limb movements	Gabapentin, elemental iron, clonazepam	Drowsiness (with gabapentin and clonazepam), constipation and abdominal discomfort (with iron)

oxybate ( $\gamma$ -hydroxybutyrate) is recommended, since this medication targets both cataplexy and sleepiness.<sup>21</sup>

A potential disadvantage of  $\gamma$ -hydroxybutyrate is the potential for misuse and drug diversion related to its central nervous system depressant qualities, similar to those of alcohol and benzodiazepines. When it comes to illicit use, the acronym GHB is used, whereas for appropriate medical use in narcolepsy, the term sodium oxybate is applied.<sup>22</sup> The dispensing of sodium oxybate is tightly regulated, and the drug is shipped to the patient only through a centralized pharmacy. Tricyclics, SSRIs, and serotonin norepinephrine reuptake inhibitors (SNRIs)

such as venlafaxine are also effective against cataplexy. SSRIs and SNRIs are preferred when cataplexy occurs in conjunction with dysphoria. Most medications have side effects, with the most significant side effects listed in **Table 11-3**. Treatment guidelines for narcolepsy in children are based on expert opinion and consensus, since a sound evidence basis is currently lacking. Presently, an ongoing multicenter, placebo-controlled trial is investigating the efficacy of sodium oxybate in childhood narcolepsy-cataplexy.

### OBSTRUCTIVE SLEEP APNEA

Key features of OSA are shown in **Table 11-4**. OSA is characterized

**TABLE 11-4** Key Features of Childhood Obstructive Sleep Apnea

Feature	Details
Prevalence	Approximately 2%; increased in those with premature birth, African American ethnicity
Etiology	Adenotonsillar hypertrophy, craniofacial anomalies, neuromuscular disorders, obesity; increased predilection in patients with Down syndrome, Prader-Willi syndrome, achondroplasia, Crouzon syndrome, kyphoscoliosis, and cerebral palsy
Clinical manifestations	Snoring not consistently observed in infants and those with neuromuscular disorders; habitual snoring, mouth breathing, restless sleep, hyperhidrosis, enuresis, increased tendency for sleepwalking and teeth grinding, feeling unrefreshed upon awakening in the morning, headache, somnolence, hyperactivity and inattentiveness, mood swings, failure to thrive (in infants)
Diagnosis	Abnormal overnight oximetry (in severe cases); nocturnal polysomnography may show increased apnea-hypopnea index (reference value is less than 1 per hour in contrast to 5 per hour in adults), increased tendency for partial occlusions rather than full apneas; upper airway sleep endoscopy and cine-MRI in cases with craniofacial anomalies
Management	<p>For mild childhood obstructive sleep apnea (OSA), consider intranasal corticosteroids plus leukotriene inhibitor.</p> <p>For moderate to severe childhood OSA, consider adenotonsillectomy; repeat polysomnography 2 to 3 months after adenotonsillectomy to evaluate for residual OSA. If OSA persists, consider continuous positive airway pressure or bilevel positive airway pressure devices; consider weight reduction measures when obese.</p> <p>For intractable OSA, consider tongue base reduction surgery, genioglossus advancement, hyoid myotomy or suspension, tracheostomy, or rapid maxillary distraction.</p> <p>For infants with laryngotracheomalacia, consider supraglottoplasty.</p> <p>For infants with hypotonia-related collapse of the upper airway, consider low flow oxygen via nasal cannula (0.25–0.5 L/min).</p>

MRI = magnetic resonance imaging.

**KEY POINTS**

- Adenotonsillar hypertrophy is the most common etiology for childhood obstructive sleep apnea, followed by craniofacial anomalies, neuromuscular disorders, and obesity.
- Infants with obstructive sleep apnea may not consistently manifest snoring and often present with stridor and laryngomalacia.
- Neurobehavioral manifestations such as inattentiveness and mood swings can be clues to childhood obstructive sleep apnea.

by partial or complete upper airway occlusion, with associated impaired air exchange despite the persistence of thoracic and abdominal respiratory effort. Associated cortical arousals may occur with or without transient oxygen desaturation. In some instances, hypoventilation may also be a component because of shallow abdominal and chest wall motion. Based on community surveys, the prevalence of childhood OSA is estimated at about 2%.<sup>23</sup> Primary snoring is the mildest form of sleep-related upper airway obstruction, occurring in about 8% of children, and is characterized by snoring at least 3 nights per week without associated apnea, increased arousals from sleep, or gas exchange abnormalities.<sup>24,25</sup> As shown in **Table 11-4**, pediatric OSA differs from OSA in adults in several different ways.

The most common etiologic factors for OSA in children are adenotonsillar hypertrophy, craniofacial anomalies such as micrognathia or maxillary hypoplasia, Down syndrome (**Case 11-1**), obesity, and neuromuscular disorders such as myotonic dystrophy or congenital nonprogressive myopathies.<sup>23</sup> Infants with OSA may not consistently manifest snoring, often present with stridor and laryngomalacia, and may have a higher incidence of congenital anomalies of the upper airway, such as choanal atresia. A superimposed inflammatory component contributes to OSA as well; levels of hydrogen peroxide may be elevated in the exhaled breath of children with OSA, suggesting increased oxidative stress.<sup>27</sup> Furthermore, elevations have been found in the serum levels of proinflammatory cytokines, such as tumor necrosis factor- $\alpha$ , interleukin-6, and interleukin-8.<sup>28,29</sup>

Repetitive occlusion of the upper airway during sleep with resultant oxygen desaturation provokes cortical arousals, suppression of REM and N3

sleep, and impacts daytime alertness and behavior. The nocturnal symptoms of childhood OSA include habitual snoring, restless sleep with snort arousals, bed-wetting, excessive sweating, mouth breathing, choking sounds, and increased predisposition to parasomnias such as confusional arousals and sleepwalking. Parents may report habitual snoring that is interrupted by silent pauses, which then terminate with snorting sounds. A metabolic syndrome may develop as a consequence of recurrent oxygen desaturation and sympathetic overactivation. This is generally characterized by insulin resistance, hyperglycemia, hypertension, dyslipidemia, abdominal obesity, and proinflammatory and prothrombotic states. Neurobehavioral manifestations such as inattentiveness and mood swings can be clues to childhood OSA. The daytime symptoms of OSA include inattentiveness, impaired academic performance, hyperactivity, and sleepiness.<sup>24,27</sup> Some children with OSA may display aeroprotective maneuvers such as keeping the neck arched backward or sleeping prone on their knees and elbows. Patients with neuromuscular disorders or hypotonia from central nervous system dysfunction tend to show more severe oxygen desaturation during periods of REM sleep in the supine position.

**Diagnosis**

When clinical symptoms and signs of OSA are obvious, clinicians can use nocturnal pulse oximetry in the home environment for making the diagnosis. The normal number of oxygen desaturation events is about one per hour of sleep. Greater than three drops in oxygen saturation below the 90% level may suggest OSA. The limitation of overnight oximetry is that it has a false-negative rate of about 70%; thus, absence of oxygen desaturation episodes



## Case 11-1

A 9-year-old girl with Down syndrome presented with symptoms of nightly snoring, restless sleep, increased night awakenings, and a relapse of bed-wetting. She had also become increasingly disruptive in the classroom. Her height and weight were at the 50th and 90th percentiles, respectively, and her body mass index was 25 kg/m<sup>2</sup>.

Examination revealed 3+ enlargement of the tonsils, an enlarged tongue size, and a tendency toward mouth breathing and inattentiveness and impulsivity. A nocturnal polysomnogram showed decreases in sleep efficiency of 78% (reference value of greater than 90%) and in rapid eye movement (REM) sleep at 13% of total sleep time (reference value of approximately 20%). The apnea-hypopnea index was elevated at 5 per hour (reference value in children of 1 per hour or less). Respiratory events were predominantly REM sleep-related obstructive hypopneas and obstructive sleep apneas (OSAs). The oxygen saturation nadir was 78%. The end-tidal carbon dioxide levels were 45 mm to 58 mm, and the percent of time with end-tidal carbon dioxide levels of greater than 50 mm was 28% of the total sleep time (reference value of 25% or less).

Given the significant enlargement of the tonsils, she was referred to pediatric otolaryngology for adenotonsillectomy. Three months after surgery, her parents felt that her sleep was much improved, but that she was still snoring intermittently and remained inattentive. A repeat polysomnogram showed residual OSA with an apnea-hypopnea index of 3 per hour; she was provided a positive airway pressure (PAP) breathing device, with improvement in snoring and daytime behavior.

**Comment.** This case illustrates several issues. About 70% to 75% of children with Down syndrome develop OSA. Consequently, the American Academy of Pediatrics recommends sleep assessment for all children with Down syndrome.<sup>26</sup> OSA in Down syndrome is multifactorial and is related to a combination of the characteristic midface hypoplasia, enlarged tongue size, collapse of the hypotonic upper airway during REM sleep, tonsillar/adenotonsillar hypertrophy, and sleep-related hypoventilation. End-tidal carbon dioxide monitoring is essential in pediatric polysomnography because oxygen desaturation is not consistently seen, and shallow breathing or hypoventilation is common. Reference values for pediatric OSA differ from those of adults (ie, the normal apnea-hypopnea index in children is 1 per hour or less, in contrast to less than 5 per hour in adults). While adenotonsillectomy reduced the severity of OSA in this patient, she ultimately required a continuous PAP (CPAP) device to alleviate residual sleep apnea. Successful use of PAP devices in children with neurologic impairments is feasible but challenging owing to decreased patient comprehension and anxiety. It requires a gradual process of desensitization for mask and CPAP equipment over several weeks, utilizing the assistance of trained nursing staff or respiratory therapists.

does not exclude OSA. Regardless, the test is helpful in facilitating diagnosis, at least in those with severe OSA. Nocturnal polysomnography is indicated when the diagnosis is uncertain. However, correlation between the presence

of clinical symptoms of OSA and polysomnographic findings is low, especially in infants. In this age group, clinical symptoms may not be consistently present, and the clinician may need to have a low threshold for ordering

**KEY POINT**

- Adenotonsillectomy is often the first step in management for obstructive sleep apnea in children and adolescents.

polysomnography. Polysomnography is indicated when patients with neurodevelopmental disabilities such as Down syndrome, epilepsy, or cerebral palsy present with restless or unrefreshing sleep. Polysomnography is also indicated when the patient should be given a nonsurgical treatment, such as a positive airway pressure (PAP) device.<sup>30</sup> Polysomnography helps distinguish OSA from obstructive hypoventilation (the latter shows an end-tidal carbon dioxide level of greater than 50 mm for 25% of the recording time or more) and in identifying central sleep apnea. The severity of the sleep-disordered breathing can also be quantified using the apnea-hypopnea index (number of apneas or hypopneas per hour of sleep). The pediatric otolaryngologist can conduct drug-induced endoscopy of the upper airway to assess the sites of upper airway occlusion in sleep.

**Management**

Mild OSA (an apnea-hypopnea index of less than 3 per hour) is treated with topical nasal corticosteroids at bedtime. In a randomized double-blind crossover trial of intranasal budesonide (32 mcg in each nostril at bedtime) for the treatment of mild OSA, significant improvement was shown in polysomnographic measures and adenoid size after 6 weeks in 48 children who received the topical steroid in comparison to 32 subjects on the placebo arm.<sup>31</sup>

For moderate (an apnea-hypopnea index of 3 to 9 per hour) or severe OSA (an apnea-hypopnea index of more than 10 per hour), the first step in management is usually adenotonsillectomy, to which most patients respond favorably. Children younger than 3 years of age, children who have craniofacial anomalies, or those with severe OSA (eg, an apnea-hypopnea index of greater than 10 per hour)

constitute high-risk groups and should be monitored carefully in the postoperative period for respiratory compromise because of upper airway edema. A clinical and, if necessary, polysomnographic reevaluation should occur 2 to 3 months after adenotonsillectomy. Behavior, quality of life, and polysomnogram findings show significant improvement when adenotonsillectomy is provided early following initial presentation, as compared to watchful waiting.<sup>32</sup> Supraglottoplasty is indicated in infants with stridor and poor weight gain during infancy. In children weighing more than 14 kg (30.8 lb), if residual OSA occurs, a PAP breathing device should be considered. PAP devices are approved for use by the US Food and Drug Administration (FDA) in children weighing more than 14 kg (30.8 lb). A variety of masks and pressure delivery devices are now available. The sleep-related obstructive hypoventilation of neuromuscular disorders may require bilevel PAP to provide noninvasive ventilation.<sup>33</sup> Weight-reduction measures are indicated in patients who are obese. Orthodontic consultation and oral appliances to pull the jaw and tongue forward in sleep are indicated in those with retrognathia and tongue prolapse. Rapid maxillary distraction is a nonsurgical technique used in children with OSA who have a high arched palate and consequent narrowing of the nasal passages. This procedure opens up the suture between the two edges of the hard palate, promotes local bone development, and flattens the shape of the palate, thus indirectly increasing the diameter of the nasal passages.<sup>34,35</sup>

**RESTLESS LEGS SYNDROME**

Based on a survey of 10,523 families from western Europe and the United States, the prevalence of RLS (also

referred to as Willis-Ekbom disease) in childhood is estimated at about 2%.<sup>36</sup> Between 25% and 40% of adult subjects with RLS report onset of symptoms in childhood or adolescence. Although, among adults, the disorder is more common in women, the childhood form of RLS is equally common in boys and girls and occurs worldwide.

## Clinical Features

The current diagnostic criteria for RLS are summarized in **Table 11-5**.<sup>37</sup> RLS is a sensorimotor disorder characterized by a discomfort in the extremities that appears in the afternoon or late evening. RLS is worsened by keeping the limbs still and relieved momentarily by movement. Children commonly describe this uncomfortable sensation as a feeling of “bugs crawling,” “owies,” “ouchies,” or “tickles” in the legs (**Case 11-2**).

When inquiring about RLS in a child, it is important to use child-appropriate terms. Children may describe a “need to move” or “need to kick the legs.” Encouraging children to depict their leg discomfort in drawings also enables diagnosis.<sup>38</sup> In preschool-age children, home video observations may reveal a pattern of

repetitive leg kicking and rubbing one leg against the other.<sup>39</sup> Nocturnal polysomnography may be required in nonverbal children for the documentation of PLMs, a finding that is present in approximately 80% of children and adults with RLS. PLMs constitute an important endophenotype for RLS.<sup>40</sup> They are defined as a series of four or more electromyographically identified limb movements that last 0.5 to 5 seconds and occur at intervals of 5 to 90 seconds, typically in non-REM sleep. The physiologic PLM index (movements per hour of sleep) is less than 5 per hour. The partial arousals triggered by PLMs may activate non-REM parasomnias such as confusional arousals or sleepwalking. Frequent arousals from the accompanying sensory discomfort or motor disturbance may lead to daytime fatigue and inattentiveness. An overlap occurs between attention deficit hyperactivity disorder and RLS.<sup>25</sup>

The term *growing pains* refers to a set of etiologically heterogeneous symptoms of discomfort in the lower extremities in children that may include musculoskeletal, arthritic, and RLS symptoms. A subset of children with growing pains may indeed have

## KEY POINTS

- Child-appropriate language should be used when inquiring about symptoms of restless legs syndrome.
- An overlap between attention deficit hyperactivity disorder and restless legs syndrome exists.

**TABLE 11-5** Considerations in the Diagnosis of Childhood-Onset Restless Legs Syndrome<sup>a</sup>

- ▶ Patient has an urge to move the limbs that may be accompanied by an uncomfortable or unpleasant sensation in the legs<sup>b</sup>
- ▶ This urge is made worse during periods of rest or inactivity
- ▶ The urge to move the limbs and the uncomfortable or unpleasant sensation accompanying it are relieved partially or totally by movement<sup>c</sup>
- ▶ The urge to move the limbs and the accompanying uncomfortable sensation are worse in the evenings<sup>d</sup>

<sup>a</sup> Data from Picchetti D, et al. Sleep Med.<sup>37</sup> [sleep-journal.com/article/S1389-9457\(13\)01070-8/fulltext](http://sleep-journal.com/article/S1389-9457(13)01070-8/fulltext).

<sup>b</sup> For children, the description of discomfort must be in the child's own words (eg, “owies”).

<sup>c</sup> Mimics of restless legs syndrome that should be considered include myalgia, leg edema, arthritis, and leg cramps.

<sup>d</sup> When symptoms are severe, symptoms may not show worsening at night.

**KEY POINT**

- Children with restless legs syndrome generally have a strong family history for restless legs syndrome.

**Case 11-2**

A 9-year-old boy presented with difficulty falling and staying asleep, a problem he had experienced for 4 years. At his bedtime of 8:00 PM or 8:30 PM, the child would be sleepy, but was unable to fall asleep for up to an hour. He indicated a discomfort in his legs around bedtime as well as an urge to stretch and move his legs; keeping his legs still was uncomfortable. The patient intermittently experienced periods of sleepwalking, which occurred 2 to 3 hours after initial sleep onset. He also had attention deficit hyperactivity disorder. His mother had experienced similar symptoms in her childhood. His general physical and neurologic examinations were normal.

A nocturnal polysomnogram showed total recording time of 436 minutes, total sleep time of 401 minutes, the periodic limb movement index was elevated at 49 (reference value of less than 5 per hour), and the apnea-hypopnea index was normal at 1 per hour, as was oxygen saturation and end-tidal carbon dioxide. The relative percentages of various sleep stages were normal. The hemoglobin was 11.8 g/dL, hematocrit was 34%, mean corpuscular volume was 77  $\mu\text{m}^3$ , and serum ferritin was 18 ng/mL.

The boy had iron deficiency that was treated with ferrous sulfate tablets 325 mg/d. Gabapentin 100 mg at bedtime was added to provide symptomatic relief from the sensory discomfort of restless legs syndrome (RLS). Concurrent with a rise in the serum ferritin level to 39 ng/mL, the sleep quality improved over the next 2 to 3 months.

**Comment.** Childhood-onset RLS may manifest as sleep initiation difficulty. Children of this age have limited ability to articulate their RLS symptoms. Polysomnography may be needed for documentation of elevated PLMs in sleep. Also, the use of child-appropriate terms in eliciting RLS history is recommended. For instance, asking about “owies” or “ouchies” in the legs will better elicit the sensory disturbance of RLS in children. A history of RLS is present in close to 75% of family members; hence, it is important to inquire about this. Systemic iron deficiency is the most common etiology for childhood RLS, so iron replacement therapy may need to be considered when children have iron insufficiency. The symptomatic improvement with oral iron may take several months. The target value of serum ferritin is about 50 ng/mL to 60 ng/mL. Gabapentin is a useful “bridge” during this period for providing symptomatic relief from the sensory discomfort. Finally, one should recognize the occurrence of attention deficit hyperactivity disorder in 30% to 40% of children with RLS.

RLS based on detailed clinical and polysomnogram assessment for increased PLMs.<sup>41</sup> Polysomnography is needed as an aid for diagnosis in nonverbal children as they may not be able to clearly articulate the nature of their symptoms. One historical clue to clinically distinguish possible causes of growing pains is that rest and immobility will worsen RLS but relieve musculoskeletal causes.

**Pathophysiology**

Genetic susceptibility, autosomal dominant mode of transmission, central nervous system iron deficiency, and dysregulation of dopaminergic neurotransmission all seem to play a role in causation of RLS. Children with RLS generally have a strong family history of the disorder in close to 75% of first-degree relatives.<sup>42</sup> An element of anticipation may exist, consistent with the

dominant mode of inheritance. In contrast, the inheritance pattern in adults with RLS is likely polygenic.<sup>43</sup> A study of linkage and genotype analysis done exclusively in 23 German children with RLS using 38 microsatellite markers found an association of RLS with susceptibility loci on *MEIS1*, *SKOR1*, and *MAP2K5* genes, but not *BTBD9*.<sup>44</sup> The results of this study are difficult to compare with those of genome-wide association studies in adults because of the small number of subjects and limited number of markers studied.

Systemic iron deficiency is a common predisposing factor for RLS and PLMs in children. A probable association exists between reduction in the serum ferritin and frequency of PLMs per hour of sleep; patients with serum ferritin levels of less than 50 ng/mL showed a significantly higher PLM index as compared to those with levels greater than 50 ng/mL.<sup>44,45</sup> The PLM index decreased following oral iron replacement therapy. Iron is a cofactor for tyrosine hydroxylase, a rate-limiting step in the conversion of tyrosine to dopamine. Further support for the role of dopaminergic neurotransmission in the pathogenesis of RLS is that dopamine receptor agonists such as ropinirole or pramipexole alleviate symptoms of RLS in adults. Secondary RLS from conditions such as peripheral neuropathy, diabetes mellitus, chronic renal disease, and spinal cord lesions is less common in children than in adults.

## Management

Assessment of serum ferritin is indicated in initial assessment of children with RLS. Levels of ferritin below 30 ng/mL to 35 ng/mL may be associated with RLS. Serum ferritin is an acute phase reactant, so caution must be exercised in interpreting the result if the blood sample has been drawn

during a systemic infection, as the level may be falsely elevated. Medication history should also be sought, especially for those that tend to exacerbate RLS such as risperidone, SSRIs, diphenhydramine, and antiemetics such as metoclopramide. When possible, medications that may worsen RLS should be either discontinued or changed to a drug less likely to aggravate symptoms.

Systematic studies on the treatment of RLS in children are lacking. Evidence about the efficacy of certain pharmacologic agents is based on anecdotal observations. The first step in treating childhood RLS is generally the correction of systemic iron deficiency.<sup>46</sup> Oral iron tablets or solutions of ferrous sulfate or ferrous gluconate are commonly used. The recommended dose of the oral iron supplement is 3 mg/kg/d to 6 mg/kg/d. Side effects of oral iron include constipation, dark stools, and abdominal discomfort. Correction of iron deficiency may take weeks or months; hence, it is important to counsel family members to be patient for improvement of levels, which should be reassessed to ensure satisfactory recovery. In case of intolerance to oral iron, IV iron sucrose can be administered in a bolus of 3 mg/kg to 6 mg/kg, with the dose not exceeding 120 mg to 150 mg,<sup>47</sup> which leads to a prompt rise in the serum ferritin level. In the interim, symptomatic relief from the discomfort of RLS can be provided by a low dose of an agent such as gabapentin (50 mg to 100 mg at bedtime). Light exercise in the evening is helpful in some subjects with RLS, but firm evidence from clinical studies is lacking. Little available evidence exists for dopaminergic agents like ropinirole or pramipexole in older teens, and their use is on an empiric basis.

## KEY POINT

- Systemic iron deficiency is a common predisposing factor for restless legs syndrome and periodic limb movements in children.



# KEY POINTS

- Non-rapid eye movement arousal parasomnias, such as confusional arousals and sleepwalking, often occur during the first third of the night.
- Obstructive sleep apnea, restless legs syndrome, and anxiety are common precipitating factors for non-rapid eye movement sleep parasomnias.

# PARASOMNIAS

Parasomnias are episodic phenomena that interrupt sleep. Aside from affecting the child's health, the events can also disrupt the sleep of other family members. They may develop at the transition from wakefulness to sleep, during REM sleep, or during non-REM sleep. Parasomnias are most common in preschool-age children and gradually decrease in incidence over the first decade.

In a large prospective study, approximately 1000 children between the ages of 2.5 and 6 years were followed longitudinally.<sup>48</sup> The overall prevalence rate was 39.8% for sleep terrors, 25% for sleep enuresis, and 14.5% for sleepwalking. The occurrence of parasomnias in preschool-age children was ubiquitous; 88% of the cohort manifested at least one parasomnia during the study period.

Non-REM sleep parasomnias include confusional arousals, sleep terrors, and sleepwalking.<sup>49</sup> They are also termed *disorders of arousal*, as they result from incomplete arousal from non-REM sleep. Typically, these events occur at the transition from deep non-REM (sleep stage N3) sleep into the lighter stages of non-REM sleep (sleep stages N2 or N1) or wakefulness. Most are likely to occur during the first third of night, as N3 sleep is most prevalent at this time.

Confusional arousals are more likely to occur in children between 2 and 5 years of age. The child will abruptly awaken within 2 to 3 hours of sleep onset, sit up in bed, and moan or cry out while appearing confused and only partially responsive to verbal commands. Autonomic dysfunction in the form of sweating, flushed face, or piloerection is minimal. The duration of the events is 5 to 20 minutes, during which the child remains inconsolable, much to the distress of the

parents. On the following morning, however, the child may have no recollection of the event at all.

Sleep terrors (night terrors) also occur within 2 to 3 hours of sleep onset, out of N3 sleep. Abrupt crying, screaming, sweating, piloerection, and agitation can occur. The patient becomes extremely agitated for several minutes, once again with amnesia for the event in the morning.

Sleepwalking is another non-REM sleep parasomnia; the patient may simply sit up in bed or climb out of bed and wander about the room or house and carry out nonpurposeful activities with no recollection of the events the following morning.

These three non-REM sleep parasomnias show a genetic predisposition. OSA, RLS, gastroesophageal reflux, and anxiety may also act as precipitating factors by activating partial arousals from sleep.

Non-REM sleep parasomnias most frequently arise during N3 sleep, but can sometimes be mistaken for nocturnal frontal lobe seizures, which are instead most frequent during N1 or N2 sleep. Seizures are typically much briefer in duration (seconds) and occur randomly through the night during N1 or N2 sleep. Nocturnal polysomnography with a 16-channel EEG montage may sometimes be required to confirm the diagnosis of non-REM sleep parasomnias and exclude nocturnal epilepsy.

The management of non-REM sleep parasomnias includes treating any underlying triggering factors for additional arousal, such as OSA or RLS. Troublesome, recurrent non-REM sleep parasomnias may require prophylaxis with clonazepam for 4 to 6 months as it seems to decrease the tendency for partial arousals from sleep. Environmental safety measures such as dead bolts and motion sensors may be necessary

in severe cases of sleepwalking to prevent injury.

## Nightmare Disorder

The *ICSD-3* defines nightmares as “recurrent episodes of awakening from sleep with recall of intensely disturbing dream mentation, usually involving fear or anxiety, but also anger, sadness, disgust, and other dysphoric emotions.”<sup>49</sup> Generally, full alertness occurs immediately upon awakening after a nightmare with intact recall of the dream experience. Additionally, the patient may have a delayed return to sleep after the episode. The description of dreams in preschool-age children may be simple and, in older children, may be more elaborate. Posttraumatic stress disorder is associated with dream content that may be distressing, with themes of inflicted violence, death, or separation from close family members.<sup>50</sup> As muscle tone and mobility are actively inhibited during REM sleep, bodily movement is rare. Physical, emotional, or sexual abuse may underlie recurrent nightmares in children. Separation anxiety or generalized anxiety disorder are other predisposing factors. Recurrent nightmares require psychological evaluation to assess for anxiety, stress, and other potential underlying factors. Actigraphy and sleep logs may reveal prolonged initial sleep latency, increased nocturnal activity, and sleep fragmentation.<sup>51</sup> Cognitive-behavioral therapy is indicated in cases of intense, disturbing nightmares. Reassurance and rescripting the content of dreams to a more pleasant ending (so-called dream image rehearsal therapy) may also be helpful.

## Rapid Eye Movement Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is characterized by aggressive or violent

motor dream enactment accompanied by REM sleep without atonia seen on polysomnography. RBD is infrequent during childhood, but may be seen as an ancillary manifestation accompanying narcolepsy or in association with various neurodevelopmental disorders, brainstem lesions, or following administration of SSRIs in younger individuals, including children and adolescents.<sup>52,53</sup> As in adults, the patient will show motor dream enactment in sleep and may yell out, kick, or flail the extremities. A cosleeping adult or sibling may be the target of the aggressive motor behavior. Unlike in adults, however, no recognized association exists with degenerative disorders such as synucleinopathies. The nocturnal polysomnogram shows preserved muscle tone in REM sleep at baseline, with episodic tendencies for motor dream enactment. Melatonin in a dose of 1 mg to 3 mg at bedtime, clonazepam 0.25 mg to 0.5 mg at bedtime, or discontinuation of predisposing medications such as antidepressants are common management approaches. For more information, refer to the article “Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias” by Birgit Högl, MD, and Alex Iranzo, MD,<sup>54</sup> in this issue of *Continuum*.

## CONCLUSION

While pediatric sleep disorders share some common features with those of adults, the constantly changing age-related normal values of sleep architecture and sleep-related breathing physiology, as well as continuous ongoing brain development, make the field challenging. Concepts of pediatric sleep medicine can be easily integrated into the practice of child neurology. Patients with epilepsy, headache, neurodevelopmental disabilities, and learning disabilities are especially likely to

### KEY POINT

■ Rapid eye movement sleep behavior disorder is infrequent during childhood, but may be seen as an ancillary manifestation accompanying narcolepsy or in association with various neurodevelopmental disorders, brainstem lesions, or following administration of selective serotonin reuptake inhibitors in younger individuals, including children and adolescents.

benefit from addressing their sleep-related comorbidities. Developments in neurophysiology, neuroimaging, and genetics are likely to inform the pathophysiology of childhood sleep-wake disorders. Sleep medicine also provides an opportunity for interaction with genomics and advancing personalized medicine.

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# Brain Circuitry Controlling Sleep and Wakefulness

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## Abstract

### Purpose of Review:

This article outlines the fundamental brain mechanisms that control sleep-wake patterns and reviews how pathologic changes in these control mechanisms contribute to common sleep disorders.

### Recent Findings:

Discrete but interconnected clusters of cells located within the brainstem and hypothalamus comprise the circuits that generate wakefulness, non-rapid eye movement (non-REM) sleep, and REM sleep. These clusters of cells use specific neurotransmitters, or collections of neurotransmitters, to inhibit or excite their respective sleep-and wake-promoting target sites. These excitatory and inhibitory connections modulate not only the presence of wakefulness or sleep, but also the levels of arousal within those states, including the depth of sleep, degree of vigilance, and motor activity. Dysfunction or degeneration of wake-and sleep-promoting circuits is associated with narcolepsy, REM sleep behavior disorder, and age-related sleep disturbances.

### Summary:

Research has made significant headway in identifying the brain circuits that control wakefulness, non-REM, and REM sleep and has led to a deeper understanding of common sleep disorders and disturbances.

## Key Points

- Different people sleep different amounts, but normal healthy adults generally sleep between 7 and 9 hours per day. However, daily sleep times vary among people and across their life spans.
- Cell groups located primarily in the brainstem and hypothalamus function to drive the individual behavioral states of sleep and wakefulness. These cell groups are mutually

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connected and use specific neurotransmitters to promote each brain state by either inhibiting or activating their respective target sites.

- Sleep is optimized when the sleep period is aligned with an individual's circadian body clock.
- Diffuse circuits located in the brainstem, hypothalamus, and basal forebrain contain glutamate, norepinephrine, histamine, serotonin, dopamine, and orexin, which serve to promote wakefulness.
- The switch from wakefulness into non-rapid eye movement sleep is facilitated and maintained by a group of neurons that inhibit arousal-promoting circuits.  $\gamma$ -Aminobutyric acid-containing cell groups located in the ventrolateral preoptic area and medullary parafacial zone function to promote and stabilize non-rapid eye movement sleep.
- Commonly used drugs can flip the sleep-wake switch toward alertness or sedation. For example, drugs that bind to  $\gamma$ -aminobutyric acid A receptors promote neuronal inhibition and sleepiness, whereas caffeine promotes wakefulness by antagonizing adenosine receptors that suppress sleep induction circuitry.
- Rapid eye movement sleep and its cardinal features (ie, cortical activation and muscle atonia) are generated by  $\gamma$ -aminobutyric acid, glutamate, and cholinergic neurons located in the brainstem.
- Identification of the brain circuits that control wakefulness and sleep has led to a deeper understanding of several sleep disorders.
- Narcolepsy is caused by loss of hypothalamic orexin cells and is characterized by excessive sleepiness, disturbed rapid eye movement sleep, sleep paralysis (atonia), and hypnagogic hallucinations.
- Cataplexy may be caused by inappropriate recruitment of circuits that generate rapid eye movement sleep paralysis.
- Cataplexy attacks are usually triggered by strong positive emotions such as excited laughter, elation, or surprise, but they are also associated with negative emotions such as fear.
- The amygdala regulates emotions and is activated during cataplexy; therefore, it may play a central role in triggering cataplexy attacks that occur in response to strong positive emotions.
- Rapid eye movement sleep behavior disorder is a parasomnia that is characterized by excessive and elaborate movements during rapid eye movement sleep.
- Rapid eye movement sleep behavior disorder is the strongest predictor of the onset of neurodegenerative diseases, with more than 80% of patients developing Parkinson disease, dementia with Lewy bodies, or multiple system atrophy.
- Degeneration of rapid eye movement sleep circuits in the brainstem underlies the motor symptoms of rapid eye movement sleep behavior disorder.
- Loss of non-rapid eye movement sleep-generating cells in the ventrolateral preoptic area is associated with sleep fragmentation during aging, and more severe loss of ventrolateral preoptic cells is associated with greater non-rapid eye movement sleep disturbance in patients with neurodegenerative disorders.

## Diagnostic Approach and Investigation in Sleep Medicine

Michael H. Silber, MBChB, FAAN. Continuum (Minneapolis Minn). August 2017; 23 (4 Sleep Neurology):973–988.

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# Abstract

## Purpose of Review:

This article provides a clinical approach to the appropriate investigation and diagnosis of sleep disorders commonly seen by neurologists.

## Recent Findings:

Home sleep apnea testing in appropriate situations can replace laboratory polysomnography in many cases of uncomplicated sleep apnea. Multiple sleep latency tests must be performed meticulously and interpreted in the clinical setting to avoid overdiagnoses of narcolepsy. Human leukocyte antigen testing has limited utility in establishing a diagnosis of narcolepsy because a positive test has low specificity. Rapid eye movement (REM) sleep behavior disorder is frequently the first manifestation of an evolving synucleinopathy, and a careful history and neurologic examination are needed to determine other early features of these disorders.

## Summary:

A meticulous history from the patient, supplemented by collateral history from an observer, is essential to establishing the diagnosis of sleep disorders. Judicious supplementary use of investigations, such as laboratory polysomnography, home sleep apnea testing, wrist actigraphy, and multiple sleep latency tests, can confirm the correct diagnosis. This article describes an approach to the sleepy patient, the patient with neuromuscular disease and possible sleep-disordered breathing, the patient with restless legs syndrome, and young and older patients with abnormal movements during sleep.

## Key Points

- Diagnoses in sleep medicine are dependent on careful and meticulous histories, which are aided by observers, and investigations should be seen as an extension of the classic clinical method, rather than independent diagnostic tools.
- Obstructive sleep apnea is the most common intrinsic cause of sleepiness, but rarer disorders must also be considered. Periodic limb movements are frequently seen on polysomnograms, but are an uncommon cause of sleepiness unless associated with restless legs syndrome.
- Differentiating sleepiness and fatigue is important, as fatigue alone is not usually due to a primary sleep disorder. An exception is that women with sleep apnea may present with fatigue rather than sleepiness.
- The first step to diagnosing hypersomnolence is to consider insufficient sleep syndrome, shift work disorder, other circadian rhythm sleep-wake disorders, or drug effects. This is best accomplished through a history supplemented as appropriate by a sleep log, wrist actigraphy, and urine drug screens.
- Assessment for sleep apnea includes taking a history of snoring, snort arousals, observed apneas, and daytime sleepiness (including scales such as the Epworth Sleepiness Scale), measuring the body mass index, and a physical examination of the palate, tongue, jaw, nose, and neck.
- Indications for home sleep apnea testing are a high pretest probability of moderate or severe obstructive sleep apnea in the absence of comorbidities such as cardiac failure, severe chronic obstructive pulmonary disease, dementia, or neuromuscular diseases affecting breathing.
- A short mean sleep latency (8 minutes or fewer) and two or more sleep-onset rapid eye movement periods on a multiple sleep latency test suggest narcolepsy, but only

if patients have adequate sleep length and normal circadian rhythmicity for at least 1 week and have discontinued psychotropic medications for at least 2 weeks.

- Because of low specificity for the diagnosis of narcolepsy, testing for the human leukocyte antigen DQB1\*0602 should be restricted to patients in whom a spinal tap for measurement of CSF hypocretin-1 concentration is contemplated.
- Patients with neuromuscular disorders should be assessed for respiratory dysfunction at all visits. Clinical screening assessments include inquiring about orthopnea and observing for paradoxical diaphragmatic movement in the supine position. Overnight oximetry may show early rapid eye movement sleep-related oxyhemoglobin desaturations.
- Restless legs syndrome is diagnosed clinically by a history of an urge to move, often associated with leg discomfort, that comes on at rest, is relieved at least temporarily by movement, and is worse in the evening or at night.
- Serum ferritin should be checked in patients with restless legs syndrome, but other tests such as polysomnography or routine nerve conduction study and EMG are generally not indicated.
- Complex nocturnal motor behaviors in a child or young adult are usually due to seizures or a non-rapid eye movement arousal parasomnia such as sleepwalking. Events that are stereotypical are more likely to be seizures.
- Polysomnography to elucidate nocturnal spells should include 16 EEG derivations and video recordings. The video associated with each arousal should be reviewed, as confusional arousals can otherwise be missed.
- Collateral history from a bed partner or caregiver is essential for the diagnosis of rapid eye movement sleep behavior disorder. Symptoms suggesting a synucleinopathy should also be elicited, and the patient should be examined for signs of parkinsonism, cognitive impairment, or dysautonomia.
- The diagnosis of rapid eye movement sleep behavior disorder requires polysomnography with submental, arm, and anterior tibial EMG derivations, and video to record any dream enactment behaviors.

# Narcolepsy and Other Central Hypersomnias

Yves Dauvilliers, MD, PhD; Lucie Barateau, MD. Continuum (Minneapolis). August 2017; 23 (4 Sleep Neurology):989–1004.

## Abstract

### Purpose of Review:

This article focuses on the clinical presentation, pathophysiology, diagnosis, differential diagnosis, and management of narcolepsy type 1 and narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, and other central disorders of hypersomnolence, as defined in the International Classification of *Sleep Disorders, Third Edition (ICSD-3)*.

### Recent Findings:

In *ICSD-3*, the names of some central disorders of hypersomnolence have been changed: narcolepsy with cataplexy and narcolepsy without cataplexy have been renamed narcolepsy type 1 and narcolepsy type 2, respectively. A low level of hypocretin-1/orexin-A in the CSF is now

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theoretically sufficient to diagnose narcolepsy type 1, as it is a highly specific and sensitive biomarker. Conversely, other central hypersomnias are less well-defined disorders with variability in the phenotype, and few reliable biomarkers have been discovered so far. The epidemiologic observation that influenza A (H1N1) infection and vaccination are potential triggering factors of narcolepsy type 1 (discovered during the 2009 H1N1 pandemic) has increased interest in this rare disease, and progress is being made to better understand the process (highly suspected to be autoimmune) responsible for the destruction of hypocretin neurons. Treatment of narcolepsy remains largely symptomatic, usually initially with modafinil or armodafinil or with higher-potency stimulants such as methylphenidate or amphetamines. Several newer wake-promoting agents and psychostimulants have also been developed, including sodium oxybate, which has a role in the treatment of cataplexy and as an adjunctive wake-promoting agent, and pitolisant, a selective histamine H<sub>3</sub> receptor inverse agonist that is currently only available in Europe.

### Summary:

Although far less common than many other sleep disorders, central hypersomnias are among the most severe and disabling diseases in the field of sleep medicine, and their early recognition is of major importance for patients, especially children, to maximize their quality of life and functioning in activities of daily living.

## Key Points

- Narcolepsy type 1 is a well-defined entity characterized by excessive daytime sleepiness and cataplexy, whereas narcolepsy type 2 is a syndrome of sleepiness without cataplexy and is a considerably less specific and more heterogeneous syndrome.
- Pathophysiologic studies have shown that narcolepsy type 1 is caused by the early loss of neurons in the hypothalamus that produce hypocretin/orexin.
- The etiology of narcolepsy type 1 is not yet completely understood, but an autoimmune process is highly suspected, with a role of genetic (human leukocyte antigen DQB1\*0602 allele) and environmental (influenza A vaccination) factors.
- Narcolepsy type 1 is associated with a wide range of sleep abnormalities and metabolic, cardiovascular, autonomic, and psychiatric consequences, in which the direct role of the hypocretin system remains to be defined.
- Treatment of narcolepsy is symptomatic and focuses on improving sleepiness and cataplexy.
- All patients with narcolepsy and central hypersomnias with uncontrolled sleepiness should be warned about the possible risks of driving while impaired and instructed not to drive when drowsy.
- Idiopathic hypersomnia is another rare central hypersomnia that has been identified more recently than narcolepsy type 1 and is probably even more rare.
- The etiology of idiopathic hypersomnia is still unknown, but homeostatic and circadian disturbances and a deficient arousal system have been suggested.
- The differential diagnosis of idiopathic hypersomnia must exclude chronic insufficient sleep syndrome, especially in long sleepers. The diagnosis of idiopathic hypersomnia requires the exclusion of other sleep, medical, and psychiatric comorbidities.
- Idiopathic hypersomnia is most frequently managed with psychostimulants, but evidence for their use in idiopathic hypersomnia remains poor, and medications are usually unsatisfactory in managing sleep inertia.



- Kleine-Levin syndrome is a recurrent hypersomnia associated with behavioral, psychological, and cognitive disturbances during episodes, with strictly normal sleep and functioning between episodes.
- Diagnostic criteria for Kleine-Levin syndrome are only clinically defined, and no reliable biomarker has yet been identified.
- The prognosis for Kleine-Levin syndrome is generally good, with a spontaneous resolution of the symptoms after a median of 14 years.
- Hypersomnia due to a medication or a substance, sleep deprivation, or a psychiatric disorder must always be considered in the differential diagnosis of narcolepsy type 2 and idiopathic hypersomnia.

## Restless Legs Syndrome and Sleep-Related: Movement Disorders

Lynn Marie Trotti, MD, MSc. Continuum (Minneapolis, Minn). August 2017; 23 (4 Sleep Neurology):1005–1016.

### Abstract

#### Purpose of Review:

This article provides an update on six sleep-related movement disorders: restless legs syndrome (RLS), periodic limb movement disorder, sleep-related leg cramps, bruxism, rhythmic movement disorder, and propriospinal myoclonus, with an emphasis on RLS.

#### Recent Findings:

RLS is a common sensorimotor disorder that impairs quality of life. RLS is frequently comorbid to neurologic, psychiatric, vascular, and inflammatory diseases. Accumulating evidence implicates the pathophysiology of RLS as a state of dopamine dysfunction and iron deficiency that occurs on a background of genetic susceptibility conferred by 6 gene polymorphisms. Multiple treatments approved by the US Food and Drug Administration (FDA) are available. Dopamine agonists and  $\alpha_2\delta$  calcium channel ligands are considered first-line treatments, but these treatments have very different side effect profiles that should be taken into consideration.

#### Summary:

Sleep-related movement disorders are frequently encountered in clinical practice. For some disorders, particularly RLS and periodic limb movement disorder, our understanding of biology, epidemiology, and treatment is advanced. For others, much work is needed to determine optimal treatment strategies.

### Key Points

- Diagnosis of restless legs syndrome requires five criteria: the urge to move the legs, worsening of symptoms with rest, worsening of symptoms in the evening or night, improvement of symptoms with movement, and symptoms that are not better explained by another condition.

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- Supportive criteria for a diagnosis of restless legs syndrome are periodic limb movements, a positive family history, and response to dopaminergic therapy.
- Periodic limb movements of sleep are seen in 80% of patients with restless legs syndrome on a single sleep study, but are also common in people without restless legs syndrome.
- The prevalence of restless legs syndrome is highest in European populations (5% to 12%), followed by Asian populations (1% to 8%). Scant data from African countries suggest a prevalence of less than 1%.
- Iron deficiency, end-stage renal disease, and pregnancy are strongly associated with restless legs syndrome. Resolution of these conditions (ie, with iron replacement therapy, renal transplant, or delivery) often improves restless legs syndrome.
- Neurologic disorders associated with restless legs syndrome include stroke, multiple sclerosis, and migraine. Psychiatric disorders associated with restless legs syndrome include depression and anxiety.
- Cross-sectional studies suggest an association between restless legs syndrome and cardiovascular disease. Restless legs syndrome might cause cardiovascular disease through increases in sympathetic activity associated with periodic limb movements of sleep (as manifested by increases in heart rate and blood pressure). Other work suggests that multimorbidity itself might increase the risk of restless legs syndrome.
- Six loci associated with the genetic risk for restless legs syndrome have been identified through genome-wide association studies. The mechanistic relationship between these genes and restless legs syndrome is under investigation, but work to date implicates genetic alterations of dopamine and iron function.
- Despite initial improvement in symptoms with dopaminergic treatment, the pathophysiology of restless legs syndrome is now suspected to reflect dopamine dysfunction rather than a hypodopaminergic state.
- Central nervous system iron deficiency is part of the restless legs syndrome pathophysiology in at least some patients, and it interacts with dopamine to exacerbate the dopamine dysfunction.
- Treatment of restless legs syndrome should include the discontinuation, if possible, of medications that exacerbate restless legs syndrome: antidepressants, antipsychotics, and metoclopramide.
- A serum iron panel should be checked in all patients diagnosed with restless legs syndrome or augmentation.
- First-line treatments of restless legs syndrome include  $\alpha_2\delta$  calcium channel ligands and dopamine agonists.
- Medication should be dosed 2 hours before typical onset of symptoms, not after symptoms have begun.
- The term *periodic limb movement disorder* should be reserved for patients who have periodic limb movements of sleep that cause sleep disruption or daytime dysfunction.
- Sleep-related leg cramps are present at least occasionally in most older adults. Quinine is no longer recommended because of serious adverse events. Alternative treatment is not well tested, but might include leg stretches at bedtime and diltiazem.
- Sleep-related bruxism may be treated with a mouth guard to prevent dental wear. Pharmacologic therapy, if necessary, may be attempted with botulinum toxin, clonidine, or benzodiazepines.
- Sleep-related rhythmic movements are ubiquitous in infants but decrease in prevalence through childhood and adulthood. Treatment with benzodiazepines is proposed for cases in which treatment is needed (eg, injury or disruption), but is not yet substantiated by clinical trial evidence.

- Hypnic myoclonus is a generally benign phenomenon seen within the first hour of sleep and is typically treated by minimizing triggers such as caffeine and stress.

# Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias

Birgit Högl, MD; Alex Iranzo, MD. Continuum (Minneapolis Minn). August 2017; 23 (4 Sleep Neurology):1017–1034.

## Abstract

### Purpose of Review:

The most common rapid eye movement (REM) parasomnia encountered by neurologists is REM sleep behavior disorder (RBD), and nightmares are so frequent that every neurologist should be able to differentiate them from the dream enactment of RBD. Isolated sleep paralysis is relatively common and is often mistaken for other neurologic disorders. This article summarizes the current state of the art in the diagnosis of RBD, discusses the role of specific questionnaires and polysomnography in the diagnosis of RBD, and reviews recent studies on idiopathic RBD as an early feature of a synucleinopathy, secondary RBD, and its management. Recent diagnostic criteria and implications of nightmares and isolated sleep paralysis are also reviewed.

### Recent Findings:

Idiopathic RBD can now be considered as part of the prodromal stage of a synucleinopathy. Therefore, an accurate diagnosis is mandatory, and this implies detection of REM sleep without atonia. The polysomnography montage, including EMG of the submental and flexor digitorum superficialis muscles, provides a high sensitivity and specificity for the diagnosis. The exact diagnosis is important for patient counseling and for future neuroprotective trials.

### Summary:

REM parasomnias include RBD, sleep paralysis, and nightmares, which have distinct clinical characteristics and different implications regarding diagnostic procedures, management, and prognosis.

## Key Points

- Although rapid eye movement sleep behavior disorder can be suspected by the patient's history, polysomnography is required for a definite diagnosis.
- Standardized protocols and normative values exist for making an exact quantitative diagnosis of rapid eye movement sleep behavior disorder.
- For accurate polysomnographic diagnosis of rapid eye movement sleep behavior disorder, polysomnography should include an EMG montage using the mentalis or submental muscle and both upper extremities (right and left flexor digitorum superficialis).

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- Patients with idiopathic rapid eye movement sleep behavior disorder have no motor or cognitive symptoms.
- Most individuals initially diagnosed with idiopathic rapid eye movement sleep behavior disorder are eventually diagnosed with Parkinson disease, dementia with Lewy bodies, and, less frequently, with multiple system atrophy.
- Patients with idiopathic rapid eye movement sleep behavior disorder show abnormalities typical of Parkinson disease such as hyposmia, depression, constipation, and decreased dopaminergic uptake in the putamen on functional imaging.
- Dysfunction in idiopathic rapid eye movement sleep behavior disorder is widespread and involves the olfactory system, the limbic system, the autonomic system, the nigrostriatal system, the hippocampus, and the cortex. These abnormalities do not occur in all subjects with idiopathic rapid eye movement sleep behavior disorder, and some individuals show only a few abnormalities, while others have many.
- In patients with idiopathic rapid eye movement sleep behavior disorder, abnormal deposits of phosphorylated  $\alpha$ -synuclein are detected in peripheral organs outside the brain.
- Rapid eye movement sleep behavior disorder may be secondary to established neurodegenerative diseases (eg, Parkinson disease, spinocerebellar ataxias), autoimmune diseases (anti-IgLON5 disease, narcolepsy, paraneoplastic syndromes), focal brainstem lesions (ischemic infarct, tumors), and may be induced by medications (antidepressants).
- Antidepressants including tricyclics, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors can induce rapid eye movement sleep behavior disorder. Lipophilic beta-blockers such as bisoprolol may also trigger rapid eye movement sleep behavior disorder.
- Rapid eye movement sleep behavior disorder has been described in the new entity, anti-IgLON5 disease, characterized by the presence of autoantibodies against IgLON5 (a neuronal cell adhesion protein), and postmortem examination shows a tauopathy involving the brainstem and hypothalamus.
- First-line drug treatment of rapid eye movement sleep behavior disorder symptoms are clonazepam or melatonin at bedtime.
- Patients with idiopathic rapid eye movement sleep behavior disorder are candidates for enrollment in neuroprotective trials.
- Nightmares are usually benign when isolated, but may be one of the features of several conditions such as rapid eye movement sleep behavior disorder, narcolepsy, sleep terrors, depression, posttraumatic stress disorder, and the effect of some medications.
- Isolated sleep paralysis is a benign condition but can be a highly frightening situation when it first occurs. Secondary sleep paralysis is a feature of narcolepsy. Relevant neurologic and medical differential diagnoses must be ruled out.
- Sleep paralysis is termed hypnagogic when it occurs upon falling asleep and hypnopompic when it occurs upon awakening.
- Ancillary respiratory muscles are also affected from rapid eye movement sleep atonia, and the diaphragm is the only respiratory muscle continuing to function during rapid eye movement sleep.
- The differential diagnosis for recurrent isolated sleep paralysis may include hypokalemic periodic paralysis, complex nocturnal visual hallucinosis, panic attacks, obstructive or central sleep apnea, and transient ischemic attack. However, the characteristic features of recurrent, short-lived, symmetrical paralysis with rapid recovery and a benign clinical course experienced only upon awakening from sleep are diagnostic historical features for recurrent isolated sleep paralysis.

# Non–Rapid Eye Movement Sleep and Overlap Parasomnias

Muna Irfan,MD; Carlos H. Schenck, MD; Michael J. Howell,MD, FAAN. Continuum (Minneap Minn). August 2017; 23 (4 Sleep Neurology):1035–1050.

## Abstract

### Purpose of Review:

This article reviews the spectrum of non–rapid eye movement (non-REM) sleep parasomnias, including sleepwalking, confusional arousals, and sleep terrors, which represent the range of phenotypic disorders of arousal from non-REM sleep that occurs in children and adults.

### Recent Findings:

The *International Classification of Sleep Disorders, Third Edition (ICSD-3)* classifies parasomnias according to the sleep stage they emerge from: REM, non-REM, or other. Demographics, clinical features, and diagnosis of non-REM parasomnias are reviewed in this article, and an up-to-date synopsis of guidelines for management strategies to assist in the treatment of these sleep disorders is provided.

### Summary:

The non-REM parasomnias are most common in children and adolescents but may persist into adulthood. They can be distinguishable from REM parasomnias and nocturnal epilepsies, and, importantly, may lead to injury. Additionally, other parasomnias in this spectrum include sleep-related eating disorder and sexsomnia. Overlap parasomnia disorder includes one or more manifestations of a non-REM parasomnia seen in combination with REM sleep behavior disorder, representing an apparent erosion of the normally distinct stages of non-REM and REM sleep. A similar yet much more extreme dissociation of states underlies *agrypnia excitata* and *status dissociatus*, which represent rare, severe dissociations between non-REM, REM, and wake states resulting clinically in oneiric behaviors and severe derangement of normal polysomnographic wake and sleep stage characteristics. Management of non-REM and overlap parasomnias and state dissociation disorders include ensuring bedroom safety and prescription of clonazepam or hypnosis, in select cases, although in children and adolescents with noninjurious behaviors, non-REM parasomnias are often age-limited developmental disorders, which may ultimately remit by adulthood, and, in these cases, counseling and education alone may suffice. Timely and accurate recognition of the non-REM and overlap parasomnias is crucial to limiting potential patient injury.

## Key Points

- Parasomnias are categorized according to the sleep stage they emerge from as rapid eye movement sleep parasomnias, non–rapid eye movement sleep parasomnias, or other (state-independent) parasomnias.
- Non–rapid eye movement parasomnias occur mostly during slow-wave sleep (sleep stage N3) but can also arise from sleep stage N2.
- Any factor increasing the propensity for sleep fragmentation (eg, pain, restless legs syndrome symptoms and periodic limb movements, obstructive sleep apnea events,

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or extrinsic stimuli such as loud noises) can lead to partial cortical arousal with impaired consciousness.

- Conditions that exacerbate disorders of arousal include those that promote the homeostatic sleep drive, such as sleep deprivation and sedating medications, by increasing the threshold for arousal.
- Confusional arousals are partial awakenings from slow-wave sleep. The individual typically sits up in a disoriented state and has some automatic behavior, such as mumbling, low-intensity vocalizations, confused motoric activity without ambulation, and sympathetic hyperactivity.
- Sleepwalking is the disorder of arousal manifesting with prominent ambulatory behavior.
- Sleep terrors consist of episodes of intense fright accompanied by loud crying or screaming in which the patient appears terrified and inconsolable. Increased autonomic activity results in tachypnea, tachycardia, mydriasis, diaphoresis, and increased muscle tone.
- Comprehensive historical accounts of witnessed events obtained from the patient and a collateral historian, especially the parents in children or a bed partner in adults, is crucial for diagnosis of parasomnia disorders.
- For pediatric parasomnias, the American Academy of Sleep Medicine suggests performing comprehensive video-polysomnography, with extended EEG and EMG montages if obstructive sleep apnea is suspected or parasomnia-related arousals are violent.
- The primary goal of managing parasomnias is to ensure the safety of the patient and cosleeper.
- Treatment of any comorbid sleep disorders, such as obstructive sleep apnea and restless legs syndrome, and removal of offending sedative agents significantly reduce the occurrence of disorders of arousal.
- Clonazepam is frequently used as a first-line agent to treat non-rapid eye movement parasomnias of disordered arousal, although other intermediate and long-acting benzodiazepines may also be used.
- For persistent episodes of sleep terrors in children, anticipatory awakenings 15 to 20 minutes before the typical time of occurrence has been shown to be highly effective in aborting the episodes.
- Sleep-related eating disorder is a condition characterized by recurrent episodes of typically amnesic binge eating of high-calorie food and sometimes bizarre pica-type ingestions after partial arousal from non-rapid eye movement sleep.
- Most researchers agree that sleep-related eating disorder is a variant of sleepwalking since it is characterized by partial or incomplete arousals from sleep, involves ambulation culminating in feeding behavior, and is affected by the usual predisposing influences for non-rapid eye movement disorders of arousal.
- Night eating syndrome is characterized by excessive eating at night before bedtime or after awakening from sleep but, unlike sleep-related eating disorder, is associated with fully preserved awareness and intentional eating.
- Dopamine agonists and topiramate have been used as pharmacotherapy for sleep-related eating disorder.
- Sexsomnia is classified as a subtype of non-rapid eye movement parasomnia disorders of arousal in the *International Classification of Sleep Disorders, Third Edition*.
- Parasomnia overlap disorder is a condition with clinical features of both non-rapid eye movement sleep parasomnias and rapid eye movement sleep behavior disorder.
- Status dissociatus is a state of complete disintegration of wake/non-rapid eye movement/rapid eye movement sleep boundaries that is without identifiable sleep stages and with behavioral and motor manifestations of oneirism (dream-enactment behaviors).

- Agrypnia excitata is an extreme form of status dissociatus, with near-continuous motor and sympathetic hyperactivity, loss of N3 sleep stage (slow-wave) architecture, and dissociation of conventional non-rapid eye movement sleep markers.

# Circadian Rhythm Sleep-Wake Disorders

Milena Pavlova, MD, FAASM. Continuum (Minneapolis, Minn). August 2017; 23 (4 Sleep Neurology):1051–1063.

## Abstract

### Purpose of Review:

The endogenous circadian rhythms are one of the cardinal processes that control sleep. They are self-sustaining biological rhythms with a periodicity of approximately 24 hours that may be entrained by external *zeitgebers* (German for time givers), such as light, exercise, and meal times. This article discusses the physiology of the circadian rhythms, their relationship to neurologic disease, and the presentation and treatment of circadian rhythm sleep-wake disorders.

### Recent Findings:

Classic examples of circadian rhythms include cortisol and melatonin secretion, body temperature, and urine volume. More recently, the impact of circadian rhythm on several neurologic disorders has been investigated, such as the timing of occurrence of epileptic seizures as well as neurobehavioral functioning in dementia. Further updates include a more in-depth understanding of the symptoms, consequences, and treatment of circadian sleep-wake disorders, which may occur because of extrinsic misalignment with clock time or because of intrinsic dysfunction of the brain. An example of extrinsic misalignment occurs with jet lag during transmeridian travel or with intrinsic circadian rhythm sleep-wake disorders such as advanced or delayed sleep-wake phase disorders. In advanced sleep-wake phase disorder, which is most common in elderly individuals, sleep onset and morning arousal are undesirably early, leading to impaired evening function with excessive sleepiness and sleep-maintenance insomnia with early morning awakening. By contrast, delayed sleep-wake phase disorder is characterized by an inability to initiate sleep before the early morning hours, with subsequent delayed rise time, leading to clinical symptoms of severe sleep-onset insomnia coupled with excessive daytime sleepiness in the morning hours, as patients are unable to “sleep in” to attain sufficient sleep quantity. Irregular sleep-wake rhythm disorder is misentrainment with patches of brief sleep and wakefulness spread throughout the day, leading to unstable sleep and waking behavioral patterns and an entirely idiosyncratic sleep-wake schedule.

### Summary:

Familiarity with these major circadian rhythm sleep-wake disorder phenotypes and their overlap with other neurologic disorders is essential for the neurologist so that clinicians may intervene and improve patient functioning and quality of life.

## Key Points

- Circadian rhythms are endogenous rhythms that control various physiologic functions and are one of the main factors that control sleep.

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- Circadian rhythms have been observed to affect a wide variety of endocrine functions, gastric acid secretion, motor activity pattern, breathing, blood pressure, as well as both normal and abnormal central nervous system activity.
- While the function of circadian rhythms is endogenous and preserved in the absence of any external cues, the timing of the biological day is regulated by multiple exogenous factors such as light, activity and physical exercise, and meal times.
- During the biological night, melatonin is secreted by the pineal gland. The onset and offset of melatonin secretion are standardly used to determine the timing of an individual's biological night.
- The secretion of melatonin requires integrity of the cervical sympathetic chain. Patients with proximal cervical trauma may have absent melatonin secretion and reduced sleep continuity.
- The frequency of certain physiologic and pathophysiologic events often exhibits a circadian rhythm.
- Analysis of interictal discharges relative to circadian phase that are measured by plasma melatonin in patients with idiopathic generalized epilepsy reveals a trend toward a circadian rhythm pattern; however, the effect of sleep is much stronger, with discharges occurring from sleep more than 8 times as frequently.
- Patients with dementia who have well-established disruptions of circadian rhythm also have an altered motor activity pattern. This may be due to extension of progressive neurodegeneration to midline brain structures involved in circadian regulation.
- Three major forms of treatment of delayed sleep-wake phase disorder are available, and these can be used in combination to achieve optimal effect: hypnotic medications, light therapy, and chronotherapy.
- Non-24-hour sleep-wake disorder is a sleep-wake rhythm disorder affecting the normal entrainment and synchronization of the patient to a 24-hour circadian rhythm.
- Patients with irregular sleep-wake rhythm disorder have difficulty synchronizing the time for sleep with societal norms for sleep times, and, as a result, they sleep during irregular periods during the day or night.

## Chronic Insomnia Disorder

Alon Y. Avidan, MD, MPH, FAAN; David N. Neubauer, MD. *Continuum (Minneapolis)*. August 2017; 23 (4 Sleep Neurology):1064–1092.

### Abstract

#### Purpose of Review:

Neurologists, along with all health care providers, commonly encounter patients with insomnia, which is a condition that impacts patients' underlying neurologic conditions in a bidirectional manner. While chronic insomnia is one of the most common sleep disturbances, only a small proportion of individuals with this condition discuss their sleep problems with their providers. When insomnia is described, it is more often in relationship to another medical problem, as opposed to an independent condition. In neurology practice, multiple factors including pain, movement disorders, sleep apnea, and medications that act on the central nervous system often contribute to insomnia. An all-inclusive approach is necessary when evaluating sleep problems in patients with insomnia.

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## Recent Findings:

The US Food and Drug Administration (FDA) has approved several medications for the treatment of insomnia that target specific receptor systems in the brain and incorporate several unique pharmacodynamic and pharmacokinetic profiles that can represent customized therapy for specific insomnia phenotypes. FDA-approved medications for insomnia include  $\gamma$ -aminobutyric acid (GABA)-modulating benzodiazepine receptor agonists, a melatonin receptor agonist, a histamine receptor antagonist, and the newest approved option, a hypocretin (orexin) receptor antagonist.

## Summary:

This article provides an evidence-based multidisciplinary approach to the treatment of insomnia, highlighting the rationale and utility of cognitive-behavioral therapy and pharmacologic interventions. Neurologists should be proactive in assessing the impact of underlying comorbidities on insomnia, particularly in the setting of psychiatric conditions such as depression, sleep disorders such as circadian rhythm disorders, and medical problems such as nocturia.

## Key Points

- Recent evidence demonstrates that poor sleep is associated with a wide range of negative health outcomes and that poorer quality of life and medical, neurologic, and psychiatric comorbidities disrupt sleep.
- Insomnia disorder refers to persistent difficulties falling asleep, maintaining sleep, or waking up earlier than habitual rise time and is associated with impairment of daytime functioning despite the opportunity for sufficient sleep duration.
- The insomnia classification by the *International Classification of Sleep Disorders, Third Edition* requires components of both nighttime and daytime elements.
- While patients with chronic insomnia tend to worry about their inability to sleep well and the negative impact this has on their lives, they often do not describe excessive daytime sleepiness.
- In the general population, about one-third of adults report intermittent symptoms of insomnia, while about 10% meet the criteria for chronic insomnia associated with daytime sequelae.
- The 3P model shows how chronic insomnia develops as a consequence of the underlying predisposing features, precipitating factors, and perpetuating processes.
- The underlying mechanism of psychophysiologic insomnia is a behaviorally based phenotype reflecting a conditioned heightened arousal associated with the bed, the environment within the bedroom (ie, clock), and maladaptive bedtime routines.
- A good general rule in the assessment of insomnia is to consider the potential etiology and likely factors that may predispose the patient to develop sleep difficulty, precipitate an insomnia episode over the clinical threshold, and perpetuate the insomnia symptoms over time once the precipitant diminishes.
- When possible, a bed partner or other family member should be interviewed to provide detailed information about any apneic spells, snoring, abnormal sleep-related movements, leg jerks, dream enactment, or behavioral abnormalities.
- Sleep questionnaires and sleep logs are very important in supplementing the formal evaluation of a patient with insomnia.
- The diversity of influences on sleep and wakefulness, extensive variability in patient expectations, along with the wide spectrum of insomnia phenotypes highlights the view that a unitary treatment pathway is not always possible.

- When managing chronic insomnia in the neurology outpatient setting, clinicians must consider the specific underlying neurologic and psychosocial comorbid conditions.
- As part of the initial assessment of insomnia, neurologists should attempt to identify and treat other sleep disorders that may lead to insomnia.
- Other comorbidities likely to manifest with insomnia include circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder, manifesting with early bedtime and early morning awakenings, and delayed sleep-wake phase disorder, resulting in difficulties initiating sleep and difficulty awakening before late morning or early afternoon.
- When managing insomnia, the initial approach should consider the potential influence of intrinsic (patient-related) and extrinsic (environmental) factors, the latter including noise, temperature, light, radio, or television.
- Sleep hygiene education is a good starting point for all patients who present with chronic insomnia because it sets the fundamental ground rules that help eradicate persistent sleep difficulty.
- While some patients have an expectation that their insomnia management would include a hypnotic medication, data demonstrate that the ideal strategy is one that specifically incorporates cognitive-behavioral therapy for insomnia.
- The core elements of cognitive-behavioral therapy for insomnia attend to components that regulate the circadian cycle, which include the underlying psychological processes that can impact sleep and the maladaptive cognitive distortions that fuel the perpetuation of insomnia.
- Pharmacotherapy for insomnia that is approved by the US Food and Drug Administration consists of agents with four distinct mechanisms of actions:  $\gamma$ -aminobutyric acid A receptor modulation, melatonin receptor agonism, histamine 1 receptor antagonism, and hypocretin/orexin antagonism.
- The benzodiazepine hypnotics are generally well tolerated, but because the distribution of  $\gamma$ -aminobutyric acid A receptors is widespread, the side effect profile is more extensive, ranging from drowsiness, dizziness, headache, and lightheadedness to ataxia and complex nocturnal behaviors, such as amnesic sleep-related eating and anterograde amnesia.
- Melatonin exerts its activity by attenuating the suprachiasmatic nucleus wake-promoting effects as opposed to actively promoting sleep.
- Compared with other histaminergic compounds, ultra-low-dose doxepin is unusual for its very high specificity and selectivity for histamine 1 receptor antagonist activity.
- Several sedating antidepressant, antipsychotic, antiepileptic, antihypertensive, and other sedating psychotropic medications are occasionally prescribed by neurologists to specifically treat insomnia symptoms.
- All the available over-the-counter sleep aids contain antihistamines, with most containing diphenhydramine or doxylamine, which are first-generation antihistamines with anticholinergic and sedative properties.
- Melatonin is a unique member of the dietary supplement sleep aid category in the United States, since it is a compound with an established role in sleep physiology and demonstrated efficacy in treating circadian rhythm sleep-wake disorders.
- The evaluation of insomnia should foster a patient-specific customized plan for management that considers the unique insomnia phenotype, chief complaint specific to the timing and chronicity of the insomnia, underlying comorbidities, sleep-wake pattern symptoms, lifestyle pattern, social habits and routines, previously tried hypnotic therapy (specific agents, dose, duration, and development of adverse effects), and any prior cognitive-behavioral therapy for insomnia.
- The cornerstone of insomnia management for all patients must include education regarding proper sleep hygiene and individualized recommendations about proper sleep-enhancing behaviors.



# Sleep-Disordered Breathing

Nancy R. Foldvary-Schaefer, DO, MS; Tina E. Waters, MD. Continuum (Minneapolis). August 2017; 23 (4 Sleep Neurology):1093–1116.

## Abstract

### Purpose of Review:

Sleep-disordered breathing encompasses a broad spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea, as well as sleep-related hypoventilation and hypoxemia. Diagnostic criteria have been updated in the *International Classification of Sleep Disorders, Third Edition* and the American Academy of Sleep Medicine *Manual for Scoring Sleep and Associated Events*. Neurologic providers should have basic knowledge and skills to identify at-risk patients, as these disorders are associated with substantial morbidity, the treatment of which is largely reversible.

### Recent Findings:

OSA is the most common form of sleep-disordered breathing and is highly prevalent and grossly underdiagnosed. Recent studies suggest that prevalence rates in patients with neurologic disorders including epilepsy and stroke exceed general population estimates. The physiologic changes that occur in OSA are vast and involve complex mechanisms that play a role in the pathogenesis of cardiovascular and metabolic disorders and, although largely unproven, likely impact brain health and disease progression in neurologic patients. A tailored sleep history and examination as well as validated screening instruments are effective in identifying patients with sleep-disordered breathing, although sleep testing is necessary for diagnostic confirmation. While continuous positive airway pressure therapy and other forms of noninvasive positive pressure ventilation remain gold standard treatments, newer therapies, including mandibular advancement, oral appliance devices, and hypoglossal nerve stimulation, have become available. Emerging evidence of the beneficial effects of treatment of sleep-disordered breathing on neurologic outcomes underscores the importance of sleep education and awareness for neurologic providers.

### Summary:

Sleep-disordered breathing is highly prevalent and grossly underrecognized. The adverse medical and psychosocial consequences of OSA and other sleep-related breathing disorders are considerable. The impact of sleep therapies on highly prevalent neurologic disorders associated with substantial morbidity and health care costs is becoming increasingly recognized.

## Key Points

- The severity of obstructive sleep apnea is determined by the apnea-hypopnea index during polysomnography, with mild obstructive sleep apnea having an apnea-hypopnea index of 5 to 14 per hour, moderate obstructive sleep apnea having an apnea-hypopnea index of 15 to 29 per hour, and severe obstructive sleep apnea having an apnea-hypopnea index of 30 or more per hour.
- Approximately 15% of adults have moderate to severe obstructive sleep apnea.

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- Women with obstructive sleep apnea have lower apnea-hypopnea indexes when matched to men for body weight, have less supine position dependency, and experience more rapid eye movement dependency of events. Women may also experience less snoring and witnessed apnea, but more insomnia and fatigue, and have lower survival rates compared to men with similar apnea-hypopnea indexes.
- A 10% increase in weight is associated with a 30% increase in the apnea-hypopnea index.
- Vast physiologic changes in obstructive sleep apnea involve complex mechanisms that increase the risk of cardiovascular and metabolic adverse outcomes via sympathetic nervous system overdrive, proinflammatory effects, enhanced thrombotic potential, and oxidative stress.
- Although self-reported instruments are available to assist in identifying high-probability obstructive sleep apnea, not everyone has a bed partner, and affected individuals may be unaware of snoring/apneic events during sleep, and patients often underestimate the degree of their daytime sleepiness and fatigue.
- Central sleep apnea, characterized by repetitive cessation of both airflow and ventilatory effort during sleep, is seen in a variety of settings, including periodic breathing in infancy, healthy adults at altitude, and Cheyne-Stokes respiration in heart failure.
- Common risk factors for central sleep apnea include an age of 65 years or older, male gender, opioid use, comorbid heart failure, stroke, atrial fibrillation, and renal failure.
- Central sleep apnea with a hypercapnic response can be seen in disorders of impaired respiratory motor control, such as in neuromuscular disorders, autonomic nervous system disorders, multiple system atrophy, motor neuron disease, and myopathies.
- Central sleep apnea with a hypocapnic response can manifest as Cheyne-Stokes respiration, which, in the setting of heart failure, differs from other causes of periodic breathing by a significantly longer cycle length (more than 40 seconds), corresponding to a prolonged circulation time.
- Sleep-related hypoventilation disorders manifest as insufficient ventilation, resulting in abnormally elevated PaCO<sub>2</sub> during sleep. Daytime awake hypoventilation, defined by a PaCO<sub>2</sub> of more than 45 mm Hg, may or may not be present. If daytime hypoventilation is present, it is further worsened during sleep.
- Patients with obesity hypoventilation syndrome have a body mass index of more than 30 kg/m<sup>2</sup> and experience alveolar hypoventilation while awake, which further worsens in sleep.
- Sleep-related hypoxemia is defined as an oxygen saturation during sleep of 88% or less in adults for at least 5 minutes in the absence of sleep-related hypoventilation on polysomnography, home sleep apnea testing, or nocturnal oximetry.
- An estimated 50% to 70% of patients with stroke have obstructive sleep apnea. Although Cheyne-Stokes respiration is highly prevalent in the initial days following acute stroke, it commonly resolves within 1 to 3 months of the acute stroke.
- Because of emergence or worsening apneas and hypopneas coinciding with vagus nerve stimulation therapy in patients with epilepsy, screening for obstructive sleep apnea and consideration of polysomnography prior to and following device implantation is recommended.
- In-laboratory polysomnography is the gold standard for the evaluation of sleep-disordered breathing and can be tailored to the clinical history (ie, expanding EEG/EMG for the evaluation of seizures and parasomnias) or combined with therapeutic titration of positive airway pressure, oxygen, oral appliances, or hypoglossal nerve stimulation.
- Home sleep apnea testing is indicated for the confirmation of obstructive sleep apnea in patients with presumed moderate to severe obstructive sleep apnea, but should not be used to screen asymptomatic patients, those with suspected mild obstructive sleep apnea,

or in patients with significant comorbid medical conditions, suspected central sleep apnea, or sleep-related hypoventilation.

- Noninvasive positive pressure ventilation is the gold standard treatment for sleep-disordered breathing. Different delivery modes are available to enhance effectiveness and adherence, the most common modality for obstructive sleep apnea being continuous positive airway pressure.
- Positive airway pressure device reimbursement requires patient compliance with the device for a minimum of 4 hours for 70% of nights in the 90 days after initiating therapy.

## Comorbid Sleep Disturbances in Neurologic Disorders

Yo-El S. Ju, MD, MSCI; Aleksandar Videnovic, MD, MSc, FAAN, FAASM; Bradley V. Vaughn, MD, FAAN, FAASM. *Continuum (Minneapolis, Minn)*. August 2017; 23 (4 Sleep Neurology):1117–1131.

### Abstract

#### Purpose of Review:

This article provides a review of disturbances of sleep comorbid with common neurologic disorders.

#### Recent Findings:

A wide variety of neurologic disorders are frequently complicated by comorbid sleep disturbances. In many cases, a bidirectional relationship appears to occur between sleep function and the neurologic disease, such that treatment of comorbid sleep disturbances may improve the symptoms of the neurologic disease.

#### Summary:

Neurologic disorders are often associated with abnormalities of sleep. Sleep influences the severity of both epilepsy and headache, and treatment of comorbid sleep disorders may improve seizure and headache frequency. Alzheimer disease is characterized by circadian phase delay and poor nighttime sleep and is strongly associated with obstructive sleep apnea. Parkinson disease is associated with several sleep disorders, including insomnia, restless legs syndrome, rapid eye movement (REM) sleep behavior disorder, daytime hypersomnia, and sleep-disordered breathing. Hypoventilation in amyotrophic lateral sclerosis and other neuromuscular disorders often presents initially with sleep problems, and treatment with noninvasive ventilation improves survival and quality of life.

### Key Points

- Seizures are more likely to start during non-rapid eye movement sleep, whereas rapid eye movement sleep appears to be protective against seizures.
- Diagnosis and treatment of comorbid sleep apnea may offer an opportunity to improve seizure frequency and quality of life in patients with epilepsy.
- Sleep deprivation and excessive sleep increase headaches in both children and adults.

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- Hypnic headaches (sometimes called alarm clock headaches) abruptly awaken patients after 1 to 3 hours of sleep and may respond to caffeine or, if frequent, treatment with lithium.
- Common sleep-wake disturbances in Alzheimer disease include nighttime insomnia, evening sundowning, and daytime sleepiness. Nighttime wandering raises safety concerns and increases caregiver burden and, therefore, is a common reason for institutionalization.
- Obstructive sleep apnea is very common in patients with Alzheimer disease, and treatment may improve cognitive symptoms.
- Sleep disorders affect the majority of patients with Parkinson disease. Sleep dysfunction in Parkinson disease is underdiagnosed by health professionals and underreported by patients.
- Sleep fragmentation is the most common sleep disturbance in Parkinson disease.
- The Parkinson Disease Sleep Scale and the Scales for Outcomes in Parkinson Disease Sleep Scale are specific to Parkinson disease and are useful in assessing sleep in patients with the disease.
- Dopaminergic medications frequently cause excessive daytime sleepiness, where the major predictive factor for excessive daytime sleepiness is not the specific type of dopaminergic agent, but rather the total dose of dopaminergic therapy.
- Excessive daytime sleepiness and sleep attacks pose significant safety issues for patients with Parkinson disease. Patients who experience sleep attacks should be advised not to drive until the issue is resolved.
- Rapid eye movement sleep behavior disorder frequently precedes the onset of cardinal diagnostic features of Parkinson disease and other  $\alpha$ -synucleinopathies.
- Rapid eye movement sleep behavior disorder is present in approximately one-third to one-half of patients with Parkinson disease and is more prevalent among patients with an akinetic/rigid phenotype and in patients who experience falls, higher disease severity, greater motor fluctuations, and an increased levodopa dose.
- Prospective studies have revealed phenoconversion rates of idiopathic rapid eye movement sleep behavior disorder to Parkinson disease in approximately 75% to 90% of patients 10 to 14 years following diagnosis of rapid eye movement sleep behavior disorder.
- Restless legs syndrome appears to be more common in Parkinson disease than in the general population and affects approximately 20% of patients with Parkinson disease. Greater severity of Parkinson disease, coexistent depression, and reduced serum iron binding capacity are risk factors for restless legs syndrome in Parkinson disease.
- Pulse oximetry is incompletely sensitive for hypoventilation, and supplemental oxygen alone is contraindicated in patients with amyotrophic lateral sclerosis and neuromuscular bellows failure, since oxygen may worsen carbon dioxide retention and lead to acute respiratory failure.
- In addition to nocturnal pulse oximetry, erect and supine spirometry, maximal inspiratory/expiratory force, sniff nasal pressure, and arterial blood gases should be obtained to assess for suspected hypoventilation in amyotrophic lateral sclerosis and other neuromuscular diseases.
- Noninvasive ventilation prolongs survival and maintains quality of life in patients with amyotrophic lateral sclerosis. Ventilation usually starts with nocturnal treatment and then expands to daytime treatment as symptoms progress.

## Sleep-Wake Disorders of Childhood

Suresh Kotagal, MD, FAAN. Continuum (Minneapolis Minn). August 2017; 23 (4 Sleep Neurology):1132–1150.

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# Abstract

## Purpose of Review:

Sleep-wake disorders occur in 10% to 28% of children and differ somewhat in pathophysiology and management from sleep-wake disorders in adults. This article discusses the diagnosis and management of key childhood sleep disorders.

## Recent Findings:

The role of sleep in memory consolidation and in the facilitation of learning has been increasingly recognized, even at the toddler stage. Cataplexy, a key feature of narcolepsy type 1, may be subtle in childhood and characterized by transient muscle weakness isolated to the face. Children with obstructive sleep apnea and restless legs syndrome display prominent neurobehavioral symptoms such as daytime inattentiveness and hyperactivity, so it is important to elicit a sleep history when these symptoms are encountered. Systemic iron deficiency occurs in about two-thirds of children with restless legs syndrome and is easily treatable. Parasomnias arising out of non-rapid eye movement (REM) sleep, such as confusional arousals and sleepwalking, may be difficult to distinguish from nocturnal seizures, and, in many cases, video-EEG polysomnography is required to differentiate between causes.

## Summary:

Clinicians should routinely integrate the assessment of sleep-wake function into their practices of neurology and child neurology because of the opportunity to improve the quality of life of their patients.

## Key Points

- The overall quantity of sleep over a 24-hour period and the temporal organization of various sleep stages evolves continuously from infancy through adolescence.
- Children experience large amounts of the N3 sleep stage, which is linked to the release of growth hormone and the consolidation of explicit memories.
- During transition from prepuberty to puberty, a shift occurs, and melatonin is released at a later time, with a corresponding delay in sleep-onset time to 10:30 PM or 11:00 PM.
- Inadequate sleep hygiene has become the foremost etiology for daytime sleepiness in adolescents.
- The sleep history should determine details regarding the sleep period, including bedtime and when sleep onset occurs for both school and non-school nights.
- The use of electronic devices is a very common contributing problem to inadequate sleep hygiene.
- The salient features of Kleine-Levin syndrome include periods of hypersomnia, inertia, and feelings of depersonalization. Hyperphagia and hypersexual behavior occur only in about 50% of patients.
- In Kleine-Levin syndrome, intercurrent viral infections may trigger a sleepiness episode, but not on a consistent basis.
- About one-third of patients with narcolepsy experience the onset of symptoms in the first or second decade of childhood.
- Children with narcolepsy may show subtle cataplexy with transient jaw weakness or head rolling, and laughter may not be a consistent trigger in children.

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- Precocious puberty and obesity are other common features accompanying the onset of narcolepsy type 1.
- Adenotonsillar hypertrophy is the most common etiology for childhood obstructive sleep apnea, followed by craniofacial anomalies, neuromuscular disorders, and obesity.
- Infants with obstructive sleep apnea may not consistently manifest snoring and often present with stridor and laryngomalacia.
- Neurobehavioral manifestations such as inattentiveness and mood swings can be clues to childhood obstructive sleep apnea.
- Adenotonsillectomy is often the first step in management for obstructive sleep apnea in children and adolescents.
- Child-appropriate language should be used when inquiring about symptoms of restless legs syndrome.
- An overlap between attention deficit hyperactivity disorder and restless legs syndrome exists.
- Children with restless legs syndrome generally have a strong family history for restless legs syndrome.
- Systemic iron deficiency is a common predisposing factor for restless legs syndrome and periodic limb movements in children.
- Non-rapid eye movement arousal parasomnias, such as confusional arousals and sleepwalking, often occur during the first third of the night.
- Obstructive sleep apnea, restless legs syndrome, and anxiety are common precipitating factors for non-rapid eye movement sleep parasomnias.
- Rapid eye movement sleep behavior disorder is infrequent during childhood, but may be seen as an ancillary manifestation accompanying narcolepsy or in association with various neurodevelopmental disorders, brainstem lesions, or following administration of selective serotonin reuptake inhibitors in younger individuals, including children and adolescents.

# Shared Medical Decision Making in Consideration of Opioid Therapy in a Patient With Restless Legs Syndrome

Michael Rubin, MD, MA

## ABSTRACT

Treating patients with restless legs syndrome (RLS) may pose a significant challenge to the clinician if those with intractable disease worsen with chronic treatment. Opioids are established as effective treatment for refractory RLS; however, some patients may be reluctant to try opioids because of the risk of dependency. Understanding the physician's duty to the patient through the framework of a shared decision-making model allows the neurologist to propose opioid therapy despite possible initial reluctance by the patient when the neurologist believes that this therapy is the most medically reasonable approach to optimizing the patient's well-being.

Continuum (Minneap Minn) 2017;23(4):1151–1155.

## Case

A 45-year-old woman presented in follow-up to her neurologist for restless legs syndrome (RLS). She experienced typical symptoms of the condition: an irresistible urge to move the legs with onset at rest that is relieved by moving the legs or getting up to walk but worsens in the evening hours. Characteristic symptoms of restless legs syndrome had begun in her early forties but had not significantly affected her daily functioning until recently. On the advice of her neurologist, she had modulated her sleep hygiene and had decreased her caffeine and alcohol intake. She had been previously treated with levodopa, dopamine agonists, gabapentin, pregabalin, iron, and benzodiazepines. While each medication helped initially, each stopped working within a short period, and her symptoms worsened, occurring earlier in the day and spreading to her arms. She was sleep deprived, experienced frequent pain, and felt perpetually frustrated. In her search for relief, she had previously pursued care at multiple sleep centers, all offering a similar diagnosis and care plan.

Her current neurologist believed she experienced augmentation, a worsening of symptoms after chronic dopaminergic drug exposure that is frequently associated with short-acting dopamine agonists and carbidopa/levodopa. Consequently, the neurologist suggested a trial of opioids. He was surprised to hear that the patient was opposed to this

*Continued on page 1152*

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*Continued from page 1151*

approach, since she seemed desperate for a solution for her debilitating condition. The neurologist had assumed she would enthusiastically endorse a new approach, especially one based on a medication class many patients with comorbid chronic pain and insomnia regularly request.

She confided that her husband had battled chronic back pain after a rock climbing accident years ago. While he still climbed regularly at a local gym, he had had multiple back surgeries and experienced a period of opiate misuse. With the support of his wife, he went through an intensive physical therapy program and began to tolerate his back pain without opioids. The patient expressed two fundamental fears about opioid therapy: first, that she would become tolerant and even dependent if she were to try opioids, and second, that her husband would be tempted into a relapse if opioids were again easily accessible in the house.

## **DISCUSSION**

### **Background**

Augmentation is a recognized complication of restless legs syndrome (RLS) treatment, and a recent task force composed of experts from the International Restless Legs Syndrome Study Group, the European Restless Legs Syndrome Study Group, and the RLS Foundation reviewed the literature to develop evidence-based recommendations to aid clinicians managing augmentation. Treating and preventing augmentation begins by removing exacerbating factors and using low-dose dopaminergic drugs but may escalate to opioid therapy in severe cases.<sup>1</sup> Even without augmentation, opioids may have a role in treating severe RLS. For example, a 2013 double-blind, randomized controlled trial of oxycodone/naloxone versus placebo showed short-term efficacy in patients who had not experienced improvement with first-line therapies.<sup>2</sup>

While opioids are effective in treating severe RLS, there is undoubtedly good reason to use them judiciously. In 2014, Franklin<sup>3</sup> described how a change in opioid prescription patterns contributed to the current opioid abuse epidemic. In 2015, Vowles and colleagues<sup>4</sup> found rates of opioid misuse of 21% to 29% (95% confidence interval, 13% to 38%) and rates of opioid addiction of 8% to 12% (95% confidence interval, 3% to 17%) among those prescribed opioids.

### **Relevant Principles**

The neurologist has a duty to guide the patient to a decision that is best for her: one that strives to meet the patient's legitimate goal of achieving relief from refractory and disabling RLS symptoms in a medically reasonable manner and a decision that is simultaneously consistent with her values. To fulfill this duty, the neurologist must acknowledge that the patient has legitimate concerns about opioid use. While the evidence-based literature may favor opioid use in cases of augmentation and refractory RLS symptoms like hers, the patient has witnessed first-hand the consequences of opioid misuse. Additionally, both clinical experience and scientific evidence confirm a real risk of dependency. Therefore, her concerns are reasonable by any evidentiary standard. Second, because neurologists are typically trained to discourage rather than encourage long-term opioid use for chronic neurologic conditions, the neurologist's path of least resistance may be never to revisit the issue of opioids with her.

However, a patient's initial resistance to a recommendation should not foreclose revisiting the recommendation if, in the neurologist's well-reasoned opinion, the benefit of the proposed intervention is of such magnitude that it affords the patient the best chance to achieve her goals in a manner consistent with her values.

Several ethical principles compel the neurologist to advocate for a medically appropriate care plan, even if doing so leads the neurologist to advocate for opioid use. Grounded in the principle of beneficence, the neurologist has a fiduciary obligation to the patient—an obligation to prioritize the patient's well-being above the neurologist's own—and advocate for a legally permissible plan likely to achieve a good outcome despite a regulatory regime or political climate, making this plan more cumbersome to execute.

Concurrently, the principle of autonomy establishes the border between a physician's vigorous but respectful advocacy for a particular course of action and paternalism. Autonomy establishes that patients with decision-making capacity have a right to self-determination. Physicians must involve their patient in a discussion of the risks and benefits of medically reasonable interventions as well as the risks and benefits of no intervention. They must respect both informed consent and informed refusal. In the "autonomy only" model of medical decision making, the conversation ends with either informed consent or informed refusal, even if the physician does not believe the patient's choice is the best option when considering the patient's goals and values. The shared decision-making model respects the patient's ultimate decision but allows the physician to have a more active role in the informed consent conversation.

### **Shared Medical Decision Making**

The process of shared medical decision making allows physicians to balance the sometimes competing imperatives of beneficence and autonomy to optimize the patient's well-being. Many different conceptualizations of shared medical decision making exist, including an approach called collaborative autonomy.<sup>5</sup> Regardless of the variation, common to all these conceptualizations is an understanding that medical decision making ought to be a collaborative process in which patients and physicians work together to arrive at an "appropriate" decision. An "appropriate" decision is one in which medical choices are made to optimize patient well-being in a manner accounting for a patient's expressed values and goals of care. Shared medical decision making still requires the physician to provide the patient with information about the disease process, the available treatments, as well as the benefits and risks of both treatment and nontreatment. The physician must ensure the patient has fully understood the options. The patient then either chooses from among the proposed treatment options or refuses treatment altogether. However, the process does not end there as it would in a pure autonomy model of medical decision making. The shared medical decision-making model creates space for the physician to express beneficence-driven concerns by advocating for the most medically advisable options in the context of the patient's expressed goals and values even if the patient has initially refused that option. Both the patient and the physician become active partners in the conversation.

Understanding that the patient in this case tried multiple classes of drugs for RLS without persistent benefit and that she had experienced significant distress

from her condition, the neurologist presented her with a clearly evidence-based therapy that she had never previously tried, opioid therapy, which she quickly, but understandably, refused. However, the shared decision-making model allows the neurologist to advocate for a trial of treatment with opioids despite the patient's initial resistance. The neurologist has already explained the risks and benefits of the intervention and has learned about the patient's goal of therapy (symptom relief) and her values (no risk of dependence or misuse). The neurologist must now acknowledge the patient's legitimate concerns about addiction risk with opioid therapy, and then, balancing her need for symptom relief with her opioid risk aversion, the neurologist should then explain why opioids may still be worth the risk, even in her particular situation.

To accomplish this goal effectively, the neurologist must reassure the patient that prescribing opioids is not an attempt to placate her or rush her out the door. The neurologist will need to spend time exploring his patient's concern about her husband's previous opioid use. Although the patient's husband is not the neurologist's patient, his needs cannot be ignored, as the health of one partner undoubtedly affects the other. The neurologist must then carefully explain why, given the challenging medical situation and her appropriate concern about addiction, opioids remain a prudent therapeutic choice. Importantly, the shared decision-making conversation in a medically and socially complex case may need to occur over a few visits. It may be worth considering a joint appointment with the patient and her husband to further assess the risk of prescribing opioids to a patient who has a spouse with a history of misuse as it may have been a particular drug or stressor that promoted his misuse, and that stressor may no longer be present. The husband may even be able to provide some reassurance to his wife that opioids in the house will not tempt him, allowing him to support her attempt to improve her quality of life.

### **Case Continued**

The neurologist asked the patient to bring her spouse to the next clinic visit to discuss the use of opioids. Using the shared medical decision-making process described above and acknowledging concerns for abuse, the patient agreed to a trial of opioid therapy. She found significant relief with her RLS, with a strict monitoring program to ensure that the opioids were used only as prescribed and with a regular evaluation for side effects and development of tolerance.

### **CONCLUSION**

The process of shared decision making may be more time consuming than a one-off discussion about a therapy, particularly when a patient is initially reluctant to consider a physician's advice. However, physicians employ the shared decision-making model routinely, even if those using it do not realize it has a formal name. For example, neurologists frequently hold multiple conversations with surrogate decision makers about either ceasing or not implementing certain critical care interventions in patients with a poor prognosis for neurologic recovery. Beneficence compels physicians to invest the requisite time to advocate for a certain course of action if that course of



action affords the best chance for patients to realize their personal goals of care. Autonomy is respected and strengthened because, through advocacy for a particular course of action, physicians use their specialized professional knowledge and skills to help patients make choices that optimize *patients'* own goals and values, not physicians' personal values. Because these conversations often become negotiations transpiring over a few conversations, physicians must be wary of complacency and not assume every conversation with a patient about a recommended therapy will inevitably lead to the patient reaching the same conclusion.

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# Driving Safety and Fitness to Drive in Sleep Disorders

Jon Tippin, MD, FAAN, FAASM; Mark Eric Dyken, MD, FAHA, FAASM, FANA

## ABSTRACT

Driving an automobile while sleepy increases the risk of crash-related injury and death. Neurologists see patients with sleepiness due to obstructive sleep apnea, narcolepsy, and a wide variety of neurologic disorders. When addressing fitness to drive, the physician must weigh patient and societal health risks and regional legal mandates. The *Driver Fitness Medical Guidelines* published by the National Highway Traffic Safety Administration (NHTSA) and the American Association of Motor Vehicle Administrators (AAMVA) provide assistance to clinicians. Drivers with obstructive sleep apnea may continue to drive if they have no excessive daytime sleepiness and their apnea-hypopnea index is less than 20 per hour. Those with excessive daytime sleepiness or an apnea-hypopnea index of 20 per hour or more may not drive until their condition is effectively treated. Drivers with sleep disorders amenable to pharmaceutical treatment (eg, narcolepsy) may resume driving as long as the therapy has eliminated excessive daytime sleepiness. Following these guidelines, documenting compliance to recommended therapy, and using the Epworth Sleepiness Scale to assess subjective sleepiness can be helpful in determining patients' fitness to drive.

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## Case

A 45-year-old woman was involved in a single-vehicle crash; she drove through oncoming traffic (fortunately missing other vehicles), continued to the opposite side of the road, and went up an embankment before stopping. She sustained only minor head and soft tissue injuries. She admitted to brief unconsciousness, recalling little until suddenly "coming to" after leaving the roadway. The incident occurred after work, which she left early because of sleepiness while doing tedious computer tasks. Her husband said she often fell asleep in front of the television and while reading. He also reported she snored so loudly, occasionally with gasping, that he no longer slept with her. Her examination was positive only for obesity, with a body mass index of 38 kg/m<sup>2</sup>, and an elevated blood pressure of 150/86 mm Hg.

## DISCUSSION

Automobile driving is an indispensable daily activity for most Americans, yet motor vehicular crashes injure millions and kill over 30,000 people every year.<sup>1</sup> Driver sleepiness is a contributing factor in many of these crashes. According to



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the American Automobile Association (AAA) Foundation for Traffic Safety, 328,000 motor vehicle crashes attributed to driver sleepiness occurred annually between 2009 and 2013.<sup>2</sup> The Foundation for Traffic Safety's estimates show that sleepy drivers were associated with 6% of crashes requiring vehicle towing, 7% of crashes necessitating treatment of an injury, 13% of crashes resulting in a hospitalization, and 21% of crashes involving a death. Moreover, sleepiness-related crashes are often more severe, with almost twice the rate of severe injuries/fatalities as compared to crashes not involving a sleepy driver. While striking, these data probably reflect the tip of the iceberg, as it may be difficult to determine if crashes are due to sleepiness if the driver and passengers do not survive. Also, some drivers may be reluctant to report fatigue or falling asleep at the wheel for fear of legal consequences. In addition, chronically sleepy drivers may not even be aware of their impairment.<sup>3</sup> While most sleepiness-related crashes are probably caused by otherwise healthy sleep-deprived drivers, this article focuses on driving safety in drivers with sleep disorders that neurologists are likely to encounter in their practices, including obstructive sleep apnea (OSA) and narcolepsy.

### **Obstructive Sleep Apnea**

The driver in the presented case very likely had OSA. The potential impact of OSA on the number of motor vehicle crashes is substantial, as it affects at least 2% to 4% of middle-aged adults in the United States.<sup>4</sup> A 2009 meta-analysis showed that drivers with OSA have a crash risk that is 2 to 3 times that of the general population.<sup>5</sup> This risk is actually attributable to a small subset of drivers with more severe disease and a history of previous sleepy driving.<sup>6,7</sup> However, individual crash risk is often difficult to determine based upon measures of disease severity (eg, apnea-hypopnea index) and subjective reports of sleepiness. Similarly, objective measures of sleepiness, such as the multiple sleep latency test (MSLT), have not proven useful in predicting crash risk in this population. Although the MSLT and maintenance of wakefulness test have been shown to correlate with simulated and closed-track driving performance,<sup>8,9</sup> conflicting data exist on the association between the MSLT and real-world outcomes in OSA drivers.<sup>10</sup> In addition to falling asleep at the wheel, drivers with OSA may crash because of cognitive dysfunction affecting sustained attention and decision making.<sup>11,12</sup>

### **Narcolepsy and Idiopathic Hypersomnia**

Narcolepsy is much less common than OSA, affecting only about 0.025% to 0.05% of people in the United States.<sup>13</sup> Drivers with narcolepsy appear to have an increased crash risk relative to the general population, although data are rather limited. Patients with narcolepsy perform less well than controls on tests of attention and in advanced driving simulators,<sup>14</sup> and a 2015 study found that they have more than twice the risk of crashing than healthy comparison drivers without narcolepsy.<sup>15</sup> However, drivers with narcolepsy treated with stimulants for more than 5 years had a crash risk no different than that of controls. Even fewer data are available concerning crash risk in idiopathic hypersomnia, a disorder of presumed central origin that is not associated with the abnormal rapid eye movement (REM) sleep features of narcolepsy. However, Philip and colleagues<sup>16</sup> found that drivers with narcolepsy and "hypersomnia" (latter not defined) had a threefold increased crash risk.

### Other Neurologic Disorders and Sleepiness

A number of neurologic disorders are associated with excessive daytime sleepiness, including restless legs syndrome/periodic limb movement disorder, myotonic dystrophy and other neuromuscular disorders, multiple sclerosis, dementia, and epilepsy.<sup>17</sup> Up to 50% of patients with Parkinson disease will report excessive daytime sleepiness, especially as the disease progresses.<sup>18</sup> Although driving performance in Parkinson disease is likely affected more by motor and cognitive impairments, excessive daytime sleepiness and “sleep attacks” have been implicated in some crashes.<sup>19</sup> Finally, many medications frequently prescribed by neurologists (eg, dopaminergic agents, benzodiazepines, hypnotics, antidepressants, opioids, anticonvulsants, and skeletal muscle relaxants) may lead to sleepiness and increased crash risk.<sup>20</sup>

### Managing the Sleepy Driver

The 2009 *Driver Fitness Medical Guidelines* for noncommercial drivers published by the National Highway Traffic Safety Administration (NHTSA) and the American Association of Motor Vehicle Administrators (AAMVA) provide useful recommendations (not legal requirements) for clinicians who must balance a driver’s privilege to remain on the road (which may be necessary for continued employment) against potential risks to the patient and the public at large (Practice Table 1).<sup>21</sup> Note that the guidelines use an arbitrary

**PRACTICE TABLE 1** Guidelines for Determining Fitness to Drive in Patients With Sleep Disorders<sup>a</sup>

Cause of Excessive Daytime Sleepiness	Acceptability for Return to Driving
<b>Obstructive Sleep Apnea</b>	
No excessive daytime sleepiness (EDS) and apnea-hypopnea index (AHI) < 20 per hour	Yes
EDS and/or AHI $\geq$ 20 per hour, CPAP adherent	Yes <sup>b</sup>
EDS and/or AHI $\geq$ 20 per hour, CPAP nonadherent	No <sup>c</sup>
<b>Narcolepsy/Hypersomnia</b>	
EDS	No
No EDS or sudden sleep onset	Yes <sup>d</sup>

CPAP = continuous positive airway pressure.

<sup>a</sup> Data from National Highway Traffic Safety Administration/American Association of Motor Vehicle Administrators, *Driver Fitness Medical Guidelines*.<sup>21</sup> [nhtsa.gov/DOT/NHTSA/Traffic%20Injury%20Control/Articles/Associated%20Files/811210.pdf](https://www.nhtsa.gov/DOT/NHTSA/Traffic%20Injury%20Control/Articles/Associated%20Files/811210.pdf).

<sup>b</sup> Positive airway pressure therapy has been shown to be an efficient treatment for obstructive sleep apnea. Clinicians should be aware that positive airway pressure therapy reaches optimal effectiveness after 2 weeks, but the effects disappear rapidly upon cessation of its use. Even a single night of noncompliance may increase crash risk.

<sup>c</sup> In the event of therapeutic noncompliance, no matter what the reason, the health care professional should counsel that driving be ceased immediately.

<sup>d</sup> Drivers with sleep disorders amenable to pharmaceutical treatment (eg, narcolepsy) may resume driving as long as the therapy has effectively eliminated excessive daytime sleepiness or the sudden onset of sleep. However, narcolepsy is a disqualifying diagnosis for commercial motor vehicle drivers regardless of response to treatment.

apnea-hypopnea index cutoff of 20 per hour despite the previously discussed data that suggest the apnea-hypopnea index is not a good indicator of crash risk. Patients on either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) should maintain an adequate level of treatment adherence, usually considered as at least 4 hours of daily use on 70% of days. The practicing neurologist can document the degree of subjective sleepiness using the Epworth Sleepiness Scale,<sup>22</sup> which can be completed in a few minutes. The Epworth Sleepiness Scale assesses global sleepiness by asking a patient to rate his or her chance of dozing in eight situations on a scale from 0 to 3, with a total score of 10 or more indicating significant sleepiness (**Supplemental Digital Content Appendix**, [links.lww.com/CONT/A222](http://links.lww.com/CONT/A222)).

The situation is more complicated for commercial motor vehicle drivers. As medical restrictions vary from state to state, neurologists should follow regulations for the states in which they practice and those their patients are licensed in. Commercial motor vehicle drivers who work across state lines are regulated by the Federal Motor Carrier Safety Administration (FMCSA) of the US Department of Transportation. Evidence-based guidelines for drivers with OSA were provided to the FMCSA by an expert medical panel and can be found on their website ([fmcsa.dot.gov/sites/fmcsa.dot.gov/files/docs/Sleep-MEP-Panel-Recommendations-508.pdf](http://fmcsa.dot.gov/sites/fmcsa.dot.gov/files/docs/Sleep-MEP-Panel-Recommendations-508.pdf)). However, these guidelines are only recommendations and have not yet been accepted as official policy. As of 2014, fitness determinations must be done only by certified examiners. The National Registry of Certified Medical Examiners may be accessed from the FMCSA website ([nationalregistry.fmcsa.dot.gov/NRPublicUI/home.seam](http://nationalregistry.fmcsa.dot.gov/NRPublicUI/home.seam)). Regarding narcolepsy, the FMCSA guidelines recommend disqualifying a commercial motor vehicle driver with the diagnosis "...regardless of treatment because of the likelihood of excessive daytime somnolence."

## **Ethical and Legal Responsibilities for Reporting Sleepy Drivers**

A physician's primary responsibility is to the patient. But what if a patient is medically noncompliant, does not adhere to CPAP, and continues to drive despite recommendations? Although physicians have a clear ethical imperative to identify at-risk patients and warn them about the risks of drowsy driving, legal requirements about reporting such drivers vary considerably from one state to the next. Currently, six states have laws requiring some form of mandatory reporting of impaired drivers, and all but two extend legal immunity to the reporting physicians (**Practice Table 2**). Sleep disorders are usually not specified, but it is reasonable to assume that conditions associated with an increased risk of falling asleep at the wheel or being inattentive because of sleepiness would qualify for reporting. An additional 42 states and Washington, DC have permissive reporting rules, and 29 of these states provide some form of immunity (civil, criminal, or both) to reporting physicians, while the remaining 14 do not. Two states have no rules on physician reporting, neither of which provide immunity to those physicians choosing to report. In total, 18 states do not provide immunity to reporting physicians. The extent of the physician's responsibility, if not mandated by state regulations, is usually satisfied by warning the patient of the risk of impaired driving. Also, a physician's exposure is diminished by documenting "standard of care," following published guidelines and practice parameters. Obviously, these are



**PRACTICE TABLE 2 Physician Reporting of Drivers by State****► States With Mandatory Reporting**

California<sup>a</sup>, Delaware<sup>a</sup>, Nevada, New Jersey, Oregon<sup>a</sup>, Pennsylvania<sup>a</sup>

**► States Allowing Permissive Reporting**

Alabama<sup>a</sup>, Alaska, Arizona<sup>a</sup>, Colorado<sup>a</sup>, Connecticut<sup>a</sup>, Florida<sup>a</sup>, Georgia<sup>a</sup>, Idaho<sup>a</sup>, Illinois<sup>a</sup>, Indiana<sup>a</sup>, Iowa<sup>a</sup>, Kansas<sup>a</sup>, Kentucky<sup>a</sup>, Louisiana<sup>a</sup>, Maine<sup>a</sup>, Maryland<sup>a</sup>, Massachusetts<sup>a</sup>, Michigan<sup>a</sup>, Minnesota<sup>a</sup>, Mississippi, Missouri<sup>a</sup>, Montana<sup>a</sup>, Nebraska<sup>a</sup>, New Hampshire, New Mexico, New York, North Carolina<sup>a</sup>, North Dakota<sup>a</sup>, Ohio, Oklahoma<sup>a</sup>, Rhode Island<sup>a</sup>, South Carolina, South Dakota, Tennessee, Texas<sup>a</sup>, Utah<sup>a</sup>, Vermont, Virginia, Washington<sup>a</sup>, Washington DC, West Virginia, Wisconsin<sup>a</sup>, Wyoming

**► States Without Specific Rules on Reporting**

Arkansas, Hawaii

<sup>a</sup> Legal immunity provided to reporting physicians.

only general guidelines, and neurologists are encouraged to seek legal opinions in the jurisdictions where they practice and the states in which their patients hold driver's licenses for a better assessment of their legal risks.

**Case Continued**

After referral for polysomnography, the patient was found to have obstructive sleep apnea and was placed on continuous positive airway pressure (CPAP) and told not to drive until adherence to effective therapy was documented. She voluntarily complied with the recommended driving restriction, but on a return visit, she asked for clearance to return to driving. She provided a 30-day download from her CPAP machine, which showed a low apnea-hypopnea index and adequate adherence with more than 70% of days with 4 hours or more of use (average 6 hours and 24 minutes). Her Epworth Sleepiness Scale score was less than 10. She was advised that she could return to driving as long as she remained adherent to treatment and did not have excessive daytime sleepiness.

**CONCLUSION**

Driving an automobile while sleepy increases the risk of motor vehicle collision-related injuries and deaths. Neurologists see patients with sleepiness in association with OSA, narcolepsy, and a wide variety of neurologic diseases. When addressing fitness to drive, the physician must weigh patient and societal health risks and regional legal mandates. Regardless of the cause, sleepy patients, especially those with a history of sleepiness-related crashes or near misses, should be counseled about the dangers of drowsy driving and told not drive if sleepy. The *Driver Fitness Medical Guidelines*, the patient's compliance to recommended therapy, and the use of the Epworth Sleepiness Scale can be helpful in determining an individual patient's fitness to drive.

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# Sleep Medicine Coding and Coverage Guidelines

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## ABSTRACT

Successful sleep billing and reimbursement is dependent on correct reporting of proper diagnostic codes for sleep disorders and associated testing. Recent changes in disease classification systems have affected the coding for sleep disorders. Guidelines set forth by the American Academy of Sleep Medicine and followed by third-party payers provide direction for the required techniques and indications for sleep procedures.

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## INTRODUCTION

The transition from the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* to the *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* and the publication of the *International Classification of Sleep Disorders, Third Edition (ICSD-3)* have all affected the coding, billing, and reimbursement of the evaluation and testing of sleep disorders.<sup>1–3</sup> Many, if not most, of the *ICD-9-CM* diagnosis codes used in sleep medicine can be crosswalked to those used in the *ICD-10-CM*. These codes contain similar descriptors and may be located in chapter 5 (mental, behavioral, and neurodevelopmental disorders), chapter 6 (diseases of the nervous system), or chapter 18 (symptoms, signs, and abnormal clinical and laboratory findings) of *ICD-10-CM*.

The American Academy of Sleep Medicine (AASM) published the *ICSD-3* in 2014, and it remains the current version. This edition, which states in its introduction that “clinicians should recognize that there is not precise concordance between the assigned codes for *ICSD-3* diagnoses and the diagnoses listed within *ICD*,”<sup>3–5</sup> continues with the tradition that more detailed classifications are generally available in *ICSD-3* than in the *ICD-10-CM*.<sup>4</sup> Notable changes in the *ICSD-3* include:

- Grouping of previous chronic insomnia diagnoses into a single chronic insomnia disorder (*ICD-10-CM* code F51.01 for primary insomnia)
- Changing the narcolepsy diagnosis descriptor to narcolepsy type 1 (with cataplexy) and type 2 (without cataplexy) (*ICD-10-CM* codes G47.411 and G47.419, respectively<sup>4</sup>)

## SLEEP PROCEDURE GUIDELINES

Guidelines for common sleep procedures are published by the AASM. Although most payers, including the Centers for Medicare and Medicaid Services (CMS), follow these guidelines in developing their coverage policies, familiarity with individual payer’s coverage guidelines is essential for reimbursement.<sup>6–9</sup> **Coding Table 1** describes common sleep procedures, and **Coding Table 2** describes the *Current*

**CODING TABLE 1 Common Sleep Procedures**

Test	Description
Actigraphy	The use of a portable, noninvasive device that continuously records gross motor movement over an extended period of time. The periods of activity and rest are indirect parameters for estimates of the periods of wakefulness and sleep of an individual.
Maintenance of wakefulness test (MWT)	A standardized objective test used to determine a person's ability to stay awake. MWT requires sleep staging of the trials that are performed at defined intervals and is attended by a qualified health care professional.
Multiple sleep latency test (MSLT)	A standard objective test of a patient's tendency to fall asleep. MSLT requires sleep staging of the nap opportunities that are performed at defined intervals and is attended by a technologist or qualified health care professional.
Polysomnography	A sleep test involving the continuous, simultaneous recording of physiologic parameters for a period of at least 6 hours that is performed in a sleep laboratory and attended by a technologist or qualified health care professional. The parameters measured are a frontal, central, and occipital EEG lead (three leads), submental EMG lead, and a left and right electrooculogram (from which sleep is staged), plus four or more additional parameters. The additional parameters typically required for polysomnography are: (1) ECG, (2) nasal and/or oral airflow, (3) respiratory effort, (4) oxyhemoglobin saturation (SpO <sub>2</sub> ), and (5) bilateral anterior tibialis EMG.

ECG = electrocardiogram; EEG = electroencephalogram; EMG = electromyogram.

*Procedural Terminology (CPT)* codes for common sleep procedures with recording requirements.

### Indications for In-laboratory–Attended Polysomnography

The AASM guidelines state that polysomnography is indicated for diagnoses of the following conditions<sup>6</sup>:

1. Sleep-related breathing disorders, continuous positive airway pressure (CPAP) titration in patients with sleep-related breathing disorders, or the assessment of treatment results in some cases
2. Narcolepsy, with a multiple sleep latency test (MSLT), in the evaluation of suspected narcolepsy
3. Parasomnias and sleep-related behaviors that are violent or otherwise potentially injurious to the patient or others
4. Sleep-related seizure disorders
5. Periodic limb movement disorder

**CODING TABLE 2** *Current Procedural Terminology (CPT) Codes for Common Sleep Procedures With Recording Requirements*

<b>CPT Codes</b>	<b>Description</b>
95800	Sleep study, unattended, simultaneous recording; heart rate, oxygen saturation, respiratory analysis (eg, by airflow or peripheral arterial tone), and sleep time
95801	Sleep study, unattended, simultaneous recording; minimum of heart rate, oxygen saturation, and respiratory analysis (eg, by airflow or peripheral arterial tone)
95803	Actigraphy testing, recording, analysis, interpretation, and report (minimum of 72 hours to 14 consecutive days of recording)
95805	Multiple sleep latency or maintenance of wakefulness testing; recording, analysis, and interpretation of physiologic measurements of sleep during multiple trials to assess sleepiness
95807	Sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, and oxygen saturation, attended by a technologist
95808	Polysomnography; any age, sleep staging with 1–3 additional parameters of sleep, attended by a technologist
95810	Polysomnography; age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist
95811	Polysomnography; age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attended by a technologist
95782	Polysomnography; younger than 6 years, sleep staging with 4 or more additional parameters of sleep, attended by technologist
95783	Polysomnography; younger than 6 years, sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attended by technologist

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ECG = electrocardiogram.

Polysomnography is not routinely indicated in the following instances<sup>6</sup>:

1. For the diagnosis of chronic lung disease
2. In cases of typical, uncomplicated, and noninjurious parasomnias when the diagnosis is clearly delineated
3. In patients with seizures who have no specific complaints consistent with a sleep disorder
4. For the diagnosis or treatment of restless legs syndrome
5. For the diagnosis of circadian rhythm sleep-wake disorders
6. For the establishment of a diagnosis of depression



The duration of polysomnography for adults (*CPT* codes 95810 and 95811) should be at least 6 hours, and for pediatric patients younger than 6 years old (*CPT* codes 95782 and 95783), the duration should be at least 7 hours.<sup>5</sup> The monitoring of polysomnography must be continuous and simultaneous. If the patient stops the study or if the study terminates for some reason, modifier 52 should be appended to the *CPT* code during billing to indicate reduced services.<sup>10</sup>

### **Indications for Out-of-Center Sleep Testing in Adult Patients**

Out-of-center sleep testing technology has been found to be comparable to polysomnography in the diagnosis of obstructive sleep apnea (OSA) in patients with a high pretest probability of moderate or greater OSA severity and no comorbid conditions. However, it is not appropriate for the diagnosis of suspected mild-severity OSA or in patients with significant comorbid medical conditions such as severe chronic obstructive pulmonary disease, cardiovascular disorders, or neuromuscular disorders, nor in patients suspected of having comorbid sleep disorders such as violent or potentially injurious parasomnia behaviors, sleep-related seizures, narcolepsy, or periodic limb movement disorder. Out-of-center sleep testing may also be indicated to monitor the response to non-CPAP treatments for sleep apnea.<sup>7</sup>

At a minimum, out-of-center sleep testing must record airflow, respiratory effort, and blood oxygenation. The AASM recommends that out-of-center sleep testing be performed under the auspices of an AASM-accredited comprehensive sleep medicine program.<sup>10</sup>

Many private providers require a follow-up visit for all patients undergoing out-of-center sleep testing. Negative or technically inadequate out-of-center sleep tests in patients with a high pretest probability of moderate to severe OSA should prompt in-laboratory polysomnography.<sup>7</sup>

### **Multiple Sleep Latency Test and Maintenance of Wakefulness Test**

The MSLT is indicated for patients with suspected narcolepsy and in patients with suspected idiopathic hypersomnia. The MSLT is not indicated for the evaluation and diagnosis of OSA, for the assessment of change following treatment with CPAP, for the evaluation of hypersomnia resulting from insufficient sleep, or for the evaluation of insomnia or circadian rhythm sleep-wake disorders.

The maintenance of wakefulness test (MWT) is indicated in the assessment of individuals where the inability to remain awake constitutes a safety issue and in patients with narcolepsy or idiopathic hypersomnia to assess response to treatment with medications.<sup>8</sup> No CMS national coverage guidelines exist for MSLT and MWT. Providers who order these tests should refer to local payer guidelines prior to performing either test.<sup>4</sup>

### **Actigraphy**

According to AASM guidelines, indications for performing actigraphy include evaluation of patients with advanced sleep-wake phase disorder, delayed sleep-wake phase disorder, shift work disorder, and suspected jet lag disorder and non-24-hour sleep-wake disorder (including that associated with blindness).<sup>9</sup> No CMS national coverage guidelines exist for actigraphy. Providers who order this test should refer to local payer guidelines prior to performing this test.<sup>4</sup>

**Positive Airway Pressure**

Positive airway pressure (PAP) devices are approved by CMS for moderate and severe OSA (an apnea-hypopnea index of greater than 15 per hour) or for mild OSA with comorbidities and symptoms including excessive daytime sleepiness, cognitive impairment, mood disorders, hypertension, ischemic heart disease, and stroke. CMS mandates an in-person follow-up visit with a physician between 31 and 90 days after initiation of CPAP therapy to review treatment adherence and benefit. During this visit, the physician must document in his or her notes that the patient is using the CPAP device for 4 hours or longer on at least 70% of nights and that the patient is benefiting from CPAP therapy.<sup>4</sup>

**Daytime Abbreviated Cardiorespiratory Sleep Study**

Some sleep physicians perform a daytime abbreviated cardiorespiratory sleep study (PAP-NAP test) in patients who have difficulty acclimating to their PAP treatment. While no specific *CPT* code exists for this particular study, code 95807-52 may be considered to indicate an attended sleep study with reduced services. Providers are encouraged to review payer policies to confirm if this is a covered service prior to performing this study. CMS and many national payer policies consider this test experimental and do not provide coverage.<sup>10,11</sup>

**TRENDS IN PAYER COVERAGE**

The financial impact of treating sleep disorders impacts the US health care system with an estimated cost of \$16 billion annually.<sup>12</sup> CMS and other payers, both nationally and locally, have implemented coverage policies intended to curb costs, such as (1) use of out-of-center sleep testing to diagnose OSA in place of in-center polysomnography, (2) use of auto-PAP to titrate patients in place of an in-center PAP titration, (3) primary care and independent diagnostic testing facilities to perform out-of-center sleep testing in place of board-certified sleep physicians, and (4) an expansion of national durable medical equipment chains, in place of local durable medical equipment providers.<sup>10</sup>

**NEW OBSTRUCTIVE SLEEP APNEA THERAPY**

In 2014, the Inspire Upper Airway Stimulation (hypoglossal nerve stimulation therapy for OSA) was approved by the US Food and Drug Administration (FDA) to treat adult patients with moderate to severe OSA who have been confirmed to fail or cannot tolerate PAP and who do not have a complete concentric collapse (as seen during drug-induced sleep endoscopy) at the soft palate level. This device is contraindicated in the following instances:

- In patients with central and mixed apneas greater than 25% of the total apnea-hypopnea index
- In patients with an anatomic finding that would affect the performance of upper airway stimulation
- In patients with a condition or who have undergone a procedure that would affect neurologic control of the upper airway
- In patients unable, or who do not have the necessary assistance, to operate the sleep remote
- In patients with an obese body mass index (ie, greater than 32 kg/m<sup>2</sup>)
- In patients who are pregnant or who plan to become pregnant

- In patients who require MRI
- In patients with an implantable device that may have unintended interactions with the Inspire therapy system<sup>13,14</sup>

Payer coverage for this treatment may be considered investigational or experimental, and clinicians should confirm coverage limitations with local payers.

## CONCLUSION

Understanding the transition from *ICD-9-CM* to *ICD-10-CM*, as well as the updated nomenclature in *ICSD-3*, are essential for physicians' evaluation and testing of sleep disorders. Knowledge of *CPT* descriptors with particular attention to their respective reporting requirements, varying national and local payer guidelines, as well as familiarity with the indications of sleep procedures, facilitates proper coding and billing, which are all essential components for third-party reimbursement.

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## Epworth Sleepiness Scale

Name: \_\_\_\_\_ Today's date: \_\_\_\_\_

Your age (yrs): \_\_\_\_\_ Your gender (Male = M, Female = F): \_\_\_\_\_

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

- 0 = **no chance** of dozing
- 1 = **slight chance** of dozing
- 2 = **moderate chance** of dozing
- 3 = **high chance** of dozing

*It is important that you answer each item as best as you can.*

### Situation

### Chance of Dozing (0-3)

Sitting and reading \_\_\_\_\_

Watching TV \_\_\_\_\_

Sitting inactive in a public place (e.g., a theater or a meeting) \_\_\_\_\_

As a passenger in a car for an hour without a break \_\_\_\_\_

Lying down to rest in the afternoon when circumstances permit \_\_\_\_\_

Sitting and talking to someone \_\_\_\_\_

Sitting quietly after a lunch without alcohol \_\_\_\_\_

In a car or bus, while stopped for a few minutes in traffic \_\_\_\_\_

_____
_____
_____
_____
_____
_____
_____
_____

**THANK YOU FOR YOUR COOPERATION**

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Contact information and permission to use:

Mapi Research Trust, Lyon, France.

Internet: <https://eprovide.mapi-trust.org>

Reference publication: Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med* 2001;2(4):297-307.

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**Sleep Neurology**

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**POSTREADING SELF-ASSESSMENT AND CME  
TEST RESPONSES**

After completing this tally sheet, please enter your answers online at [aan.com/continuum/cme](http://aan.com/continuum/cme).

- |               |               |
|---------------|---------------|
| 1. a b c d e  | 21. a b c d e |
| 2. a b c d e  | 22. a b c d e |
| 3. a b c d e  | 23. a b c d e |
| 4. a b c d e  | 24. a b c d e |
| 5. a b c d e  | 25. a b c d e |
| 6. a b c d e  | 26. a b c d e |
| 7. a b c d e  | 27. a b c d e |
| 8. a b c d e  | 28. a b c d e |
| 9. a b c d e  | 29. a b c d e |
| 10. a b c d e | 30. a b c d e |
| 11. a b c d e | 31. a b c d e |
| 12. a b c d e | 32. a b c d e |
| 13. a b c d e | 33. a b c d e |
| 14. a b c d e | 34. a b c d e |
| 15. a b c d e | 35. a b c d e |
| 16. a b c d e | 36. a b c d e |
| 17. a b c d e | 37. a b c d e |
| 18. a b c d e | 38. a b c d e |
| 19. a b c d e | 39. a b c d e |
| 20. a b c d e | 40. a b c d e |

**PATIENT MANAGEMENT PROBLEM RESPONSES**

- |              |               |
|--------------|---------------|
| 1. a b c d e | 7. a b c d e  |
| 2. a b c d e | 8. a b c d e  |
| 3. a b c d e | 9. a b c d e  |
| 4. a b c d e | 10. a b c d e |
| 5. a b c d e | 11. a b c d e |
| 6. a b c d e | 12. a b c d e |





# Postreading Self-Assessment and CME Test

Ronnie Bergen, MD; James W. M. Owens Jr, MD, PhD

The *Continuum* Postreading Self-Assessment and CME Test is an integral part of the issue that is intended to stimulate thought and help participants assess general understanding of the material presented in this issue. The Postreading Self-Assessment and CME Test is also approved by the American Board of Psychiatry and Neurology (ABPN) to meet the Lifelong Learning (CME), Self-Assessment (SA) (part 2) component for Maintenance of Certification.

For each item, select the single best response. A tally sheet is provided with this issue to allow the option of marking answers before entering them online at [aan.com/continuum/cme](http://aan.com/continuum/cme). A faxable scorecard is available only upon request to subscribers who do not have computer access or to nonsubscribers who have purchased single back issues (send an email to [ContinuumCME@aan.com](mailto:ContinuumCME@aan.com)).

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- ▶ 1. A 20-year-old woman comes to clinic after having been found in the kitchen eating a bar of soap with peanut butter smeared on it. Her partner reports that the patient appeared unaware and did not respond in her usual manner during this episode. The patient has gained 10 pounds over the past 6 months and has awakened in the morning with food on her face or under her pillow without memory of how it got there. Which of the following sleep disorders is most likely in this patient?
  - A. confusional arousal
  - B. Kleine-Levin syndrome
  - C. night eating syndrome
  - D. rapid eye movement (REM) sleep behavior disorder
  - E. sleep-related eating disorder
  
- ▶ 2. A 32-year-old woman with medically refractory epilepsy had a vagus nerve stimulation (VNS) device placed 6 months ago. The device has now been ramped up to typical settings with a normal mode output current of 1.5 mA. She has noted some improvement in her seizure frequency but has been experiencing increasing daytime somnolence. Other than epilepsy, she has been healthy and has no history of significant sleep difficulties or concern for sleep-related breathing problems. Her examination reveals a body mass index of 22 kg/m<sup>2</sup> with a normally formed oropharynx, minimal tonsillar tissue, and a Friedman grade II tongue position. Overnight polysomnography reveals obstructive sleep apnea with an apnea-hypopnea index of 18 per hour. Which of the following interventions would be best to recommend for decreasing this VNS-associated complication?
  - A. increased VNS stimulation frequency
  - B. prolonging VNS off time
  - C. referral for tonsillectomy and adenoidectomy
  - D. removal of the VNS device
  - E. repeat overnight polysomnography to titrate bilevel positive airway pressure

- 3. A 17-year-old boy has a 3-year history of recurrent episodes of hypersomnia lasting 1 to 2 weeks. During the episodes, he sleeps 14 to 18 hours per day and is very groggy when awake. He also has a significantly increased appetite and hypersexuality and eats much more than usual during the episodes. In between episodes, he has no neurologic symptoms and no sleep problems. Which of the following medications would be most likely to help prevent his periodic hypersomnia?
- A. lithium
  - B. melatonin
  - C. methylphenidate
  - D. sodium oxybate
  - E. trazodone
- 4. Which of the following exogenous factors most strongly influences circadian rhythms?
- A. exercise
  - B. light
  - C. meals
  - D. medications
  - E. noise
- 5. A 3-year-old girl is brought to her pediatrician for routine care. While at the appointment, her parents remark that it is very difficult to get her to “go down for the night,” unless she has a particular form of pacifier. If they try to take it away, she screams and refuses to go to sleep, despite the fact that her parents are very consistent in enforcing her bedtime. She otherwise has normal growth and development. She was adopted at age 2 from abroad. What is the most likely diagnosis?
- A. adjustment insomnia
  - B. behavioral insomnia, limit-setting type
  - C. behavioral insomnia, sleep-onset association type
  - D. idiopathic insomnia
  - E. separation anxiety
- 6. A 45-year-old man reports excessive sleepiness over the past 6 months. He awakens feeling unrefreshed despite getting 10 hours of sleep per night. He also reports dull holocephalic morning headaches a few times per week. Although he does not report difficulty sleeping, his bed partner reports significant snoring with several snort arousals per night, particularly when the patient is sleeping on his back. The patient is otherwise medically healthy with no chronic illnesses and takes no medications. His general physical examination reveals an overweight man with a Friedman grade IV tongue position. His neurologic examination is normal. Which of the following is the most appropriate initial investigation in this patient?
- A. direct laryngoscopy
  - B. home sleep apnea testing
  - C. overnight polysomnography
  - D. overnight pulse oximetry
  - E. pulmonary function testing
- 7. At what time of day does melatonin secretion typically peak?
- A. at sleep onset
  - B. during midday
  - C. 2 hours before normal sleep time
  - D. midway through the normal sleep time
  - E. upon awakening

- 8. A 15-year-old boy with Duchenne muscular dystrophy reports excessive daytime sleepiness that has been worsening over the past year. He is still ambulatory, although he is only able to walk short distances. He reports no change in cognitive function or mood. He has been healthy overall with no recent serious illnesses or hospitalizations. On examination, his abdomen pulls inwards slightly on inspiration when supine, and intermittent activation of accessory respiratory muscles is noted. Which of the following initial screening investigations would be most appropriate?
- A. home sleep apnea testing
  - B. multiple sleep latency test
  - C. nerve conduction study and EMG
  - D. overnight pulse oximetry
  - E. serum ferritin
- 9. As part of the evaluation of insomnia, in which of the following scenarios would it be most appropriate to order polysomnography?
- A. when no improvement occurs with hypnotics
  - B. when no person can corroborate the history
  - C. when sleep-disordered breathing is suspected
  - D. when suspicion of over-reporting exists
  - E. when the patient reports nightmares
- 10. Which of the following clinical or laboratory findings is required for making a diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD)?
- A. frequent vocalizations in sleep
  - B. observer report of dream enactment
  - C. polysomnography showing REM sleep atonia loss
  - D. severe periodic limb movements during sleep
  - E. sleepwalking in the setting of dementia
- 11. Which of the following polysomnographic findings is most likely to be seen in a patient during an attack of Kleine-Levin syndrome?
- A. decreased arousals
  - B. decreased sleep efficiency
  - C. increased EMG activity during rapid eye movement (REM) sleep
  - D. increased non-REM stage 3 sleep
  - E. increased periodic limb movements
- 12. A 40-year-old man with a history of tobacco use and obesity reports headaches for the past year. He frequently awakens in the morning with a headache, which is described as holocephalic pressure. He takes an over-the-counter headache preparation about twice a week that helps. He exercises by lifting weights. Physical examination shows an overweight man with a short, thick neck. Cranial nerves are normal and optic discs appear normal. What is the most likely diagnosis?
- A. cluster headache
  - B. exertional headache
  - C. hypnic headache
  - D. increased intracranial pressure
  - E. obstructive sleep apnea

- 13. A 55-year-old man is brought to the emergency department in an agitated state. His friends report that he does not appear to sleep but seems to be lost in a confused dream world. On examination, he is hypertensive, tachycardic, and mildly febrile. He appears agitated and frequently exhibits gestures that seem to mimic purposeful tasks, such as combing his hair or opening a jar. EEG reveals a low-voltage fast background and vertex transients without a posterior dominant rhythm appearing like a blending of rapid eye movement (REM) and sleep stage N1. Which of the following conditions is most likely to be the cause of this man's current state?
- A. alcohol withdrawal
  - B. autoimmune hepatitis
  - C. corticobasal degeneration
  - D. depression
  - E. zolpidem treatment
- 14. A 26-year-old woman reports intermittent deep discomfort in her legs that is temporarily relieved by movement. The discomfort occurs every day and is worse at night and particularly when watching television or engaging in other sedentary activities. She is otherwise healthy, takes no medications, and has no family history of neurologic disorders. Her neurologic examination is normal. Which of the following serum laboratory tests is most appropriate to order at this time?
- A. calcium
  - B. creatinine
  - C. ferritin
  - D. folate
  - E. vitamin B<sub>12</sub>
- 15. A 60-year-old man who has always been an early riser now finds that he awakens at about 4:00 AM habitually. He then generally starts working on his computer and drinks a cup of coffee. He is tired at work in the late afternoon, but does not typically use caffeine after lunchtime. He often takes naps between 7:00 PM and 8:00 PM while watching television and then usually has no difficulty falling back asleep at about 10:00 PM. Which of the following strategies should be employed as a first step to facilitate initiation of sleep?
- A. avoid late-evening napping
  - B. encourage reading in bed
  - C. forego morning coffee
  - D. trial of a short-acting hypnotic
  - E. watch television before bedtime
- 16. A 61-year-old man presents with his bed partner, who reports that he "beats me up in his sleep." Over the past 2 years, the patient has had nonstereotyped, often violent behaviors that are more frequent during the second half of the sleep period on most nights. When awakened during one episode, he reported that he was dreaming of fighting off robbers. He has remained continent throughout these episodes and does not recall anything about them the next day. He does not snore, and no snorting arousals have been noted. Which of the following findings is most likely to be present on overnight polysomnography?
- A. frequent epileptiform activity during non-rapid eye movement (REM) sleep
  - B. frequent periodic limb movements of both legs
  - C. increased EMG activity during REM sleep
  - D. obstructive apnea, worse during REM sleep
  - E. sleep-onset REM periods



- 17. Which of the following is the most common presenting symptom in narcolepsy?
- A. dream enactment
  - B. excessive daytime sleepiness
  - C. sleep paralysis
  - D. sleepwalking
  - E. unrefreshing nocturnal sleep
- 18. Which of the following therapies for restless legs syndrome (RLS) is most likely to be associated with augmentation?
- A. gabapentin
  - B. opioids
  - C. pramipexole
  - D. pregabalin
  - E. rotigotine
- 19. What is the mechanism of action of ultra-low-dose doxepin for sleep-maintenance insomnia?
- A.  $\gamma$ -aminobutyric acid A (GABA-A) receptor agonism
  - B. dopamine 2 receptor antagonism
  - C. histamine 1 ( $H_1$ ) receptor antagonism
  - D. hypocretin/orexin receptor antagonism
  - E. serotonin and norepinephrine agonism
- 20. A 9-year-old girl presents with concerns for excessive sleepiness during the day. She eats dinner around 6:00 PM, completes her homework, plays until 9:30 PM, and then turns off all electronic devices and gets to bed by 10:00 PM. She falls asleep quickly and does not have noted awakenings at night. She snores occasionally but has never been heard to have respiratory pauses, gagging, choking, or gasping. During the school year, she is awakened at 6:00 AM and is very difficult to arouse. While she doesn't usually take naps, she feels sleepy for much of the day and particularly so after lunch. On weekends, she goes to bed around 10:00 PM and is awakened around 8:30 AM, again feeling tired, but much less tired than during the week. On examination, she has a normal body mass index, normal vital signs, and a normal-appearing oropharynx. Which of the following diagnoses most likely explains this girl's excessive daytime sleepiness?
- A. delayed sleep-wake phase disorder
  - B. depression
  - C. idiopathic hypersomnia
  - D. insufficient sleep for age
  - E. obstructive sleep apnea
- 21. A 70-year-old man with a history of diabetes mellitus is referred for polysomnography because his wife reports that he kicks a great deal at night. He reports no sleep problems and denies daytime sleepiness. The study shows several episodes of periodic limb movements of sleep. Which of the following is the most appropriate next step?
- A. check hemoglobin A<sub>1c</sub>
  - B. clonazepam trial
  - C. perform a multiple sleep latency test
  - D. perform an EEG
  - E. reassure sleep partner

- 22. A 10-year-old girl has been having nocturnal episodes characterized by walking around the house in an unresponsive state. These have been occurring once or twice per week over the past several months and begin in the first 1 to 2 hours after she falls asleep. She is able to open doors and go down stairs but has also demonstrated abnormal behavior, such as urinating in her parents' closet. The episodes last for a variable period of time and end with her appearing to return to full sleep. Attempts to guide her back to her bed during an episode have been unsuccessful. She does not seem tired in the morning after these episodes and has no recollection of them. She is doing well in school. Her father had similar episodes when he was in grade school but "outgrew them." She continues to do well in fifth grade, and her general physical and neurologic examination are normal. Which of the following is the most likely diagnosis?
- A. agrypnia excitata
  - B. nocturnal frontal lobe epilepsy
  - C. periodic limb movements of sleep
  - D. rapid eye movement (REM) sleep behavior disorder
  - E. sleepwalking
- 23. A 65-year-old man presents because of disturbing behaviors during sleep. His wife states that this has been going on for many years, but that it seems to have worsened. He shouts and sometimes lashes out violently in sleep, because of which his wife now sleeps in a separate bedroom. Neurologic examination is normal. Polysomnography demonstrates loss of rapid eye movement (REM) atonia. Which of the following pharmacologic agents is most appropriate for his symptoms?
- A. amitriptyline
  - B. clonazepam
  - C. doxepin
  - D. duloxetine
  - E. paroxetine
- 24. Which of the following is the most likely etiologic mechanism for the destruction of hypocretin (orexin)-secreting neurons in patients with narcolepsy type 1?
- A. autoimmune
  - B. infectious
  - C. neoplastic
  - D. neurodegenerative
  - E. vascular
- 25. A 5-year-old girl has been having nocturnal episodes that begin with a loud scream. When her parents check on her, she is agitated, pale, tremulous, and perspiring. They used to try to console her but found that doing so seemed to make the episode last longer. After 2 to 5 minutes, the child returns to sleep, and she seems fine the next day with no recollection of anything amiss the night before. These episodes occur once every few nights. Which of the following is the most likely diagnosis?
- A. confusional arousals
  - B. nightmares
  - C. panic attacks
  - D. rapid eye movement (REM) sleep behavior disorder
  - E. sleep terrors

- 26. A 7-year-old girl is brought to clinic with episodes of awakening from sleep almost every night with recollection of dreams characterized by intense anxiety. These episodes began after a serious motor vehicle accident in which she was an uninjured passenger. She is fully awake following the dreams and can relay the content to her parents in detail. These episodes tend to happen more in the second half of the night. The patient generally falls asleep well and does not have noted nocturnal arousals outside of those following her anxious dreams. A psychological evaluation reveals no evidence of a mood disorder. Which of the following interventions would be most likely to help decrease the frequency and disturbing nature of these episodes?
- A. cognitive-behavioral therapy
  - B. fluoxetine in the morning
  - C. melatonin 4 hours before intended bedtime
  - D. scheduled awakening 15 to 30 minutes before dreams usually occur
  - E. zolpidem at bedtime
- 27. A 78-year-old man develops an abnormal respiratory pattern 24 hours after experiencing a right middle cerebral artery stroke. He exhibits a pattern of increasing and then decreasing respiratory volumes over the course of 50 to 60 seconds, followed by a pause, and then the pattern repeats. Prior to the stroke, he had no known respiratory issues. His past medical history is significant for hypertension, hypercholesterolemia, and mild cognitive impairment. What is the most likely prognosis for the patient's abnormal respiratory pattern?
- A. persist indefinitely
  - B. resolve in 1 to 3 months
  - C. resolve in 6 to 12 months
  - D. resolve in 1 to 2 years
  - E. resolve in 3 to 5 years
- 28. A 20-year-old woman with excessive daytime sleepiness and who takes frequent daytime naps also has sudden episodes of muscle tone loss triggered by sudden emotions. She undergoes overnight polysomnography, which reveals moderate sleep apnea and significant sleep fragmentation. Which of the following is the most appropriate next step?
- A. EEG
  - B. multiple sleep latency test
  - C. prescribe modafinil 200 mg in the morning
  - D. serum ferritin testing followed by iron supplementation if indicated
  - E. treat with continuous positive airway pressure (CPAP) for 1 month and then perform a multiple sleep latency test
- 29. Activation of which of the following brain regions has been linked to cataplexy?
- A. amygdala
  - B. anterior nucleus of the thalamus
  - C. caudate nucleus
  - D. hippocampus
  - E. ventral tegmental area
- 30. A 60-year-old woman has a history of painful spasms and cramps in her legs that sometimes cause her to get out of bed. She notices a grabbing feeling in the calf lasting, at times, more than 1 minute. She is otherwise healthy. Which of the following is the best treatment for her symptoms?
- A. application of heat
  - B. diltiazem
  - C. quinine
  - D. stretching exercises
  - E. transcutaneous electrical nerve stimulation

- ▶ 31. Which of the following is the most effective treatment for patients with advanced sleep-wake phase disorder?
  - A. anxiolytics in early evening
  - B. exercise in the afternoon
  - C. hypnotics during the night
  - D. light therapy in late afternoon
  - E. melatonin at night
  
- ▶ 32. Activation of which of the following brain regions is involved in generating non-rapid eye movement (REM) sleep?
  - A. locus coeruleus
  - B. orexinergic neurons of lateral hypothalamus
  - C. pontine dorsal raphe nuclei
  - D. tuberomammillary nucleus
  - E. ventrolateral preoptic area of hypothalamus
  
- ▶ 33. Which of the following therapies is most likely to be effective for reducing episodes of sleepwalking?
  - A. carbamazepine
  - B. clonazepam
  - C. pramipexole
  - D. quetiapine
  - E. topiramate
  
- ▶ 34. Which of the following disorders is most likely to be associated with central sleep apnea with a hypocapnic response?
  - A. autonomic nervous system disorders
  - B. congestive heart failure
  - C. motor neuron disease
  - D. multiple system atrophy
  - E. neuromuscular disorder
  
- ▶ 35. An 80-year-old woman with a 3-year history of Alzheimer disease is brought by her caregiver for a routine follow-up visit. The caregiver relates that she is quite tired out because the patient often gets up in the middle of night and thinks it is morning; additionally, she will doze off repeatedly during the day, such that it is hard to engage her in any activity. The patient is noted to snore when she sleeps in her recliner. Which of the following is the most likely diagnosis?
  - A. advanced sleep-wake phase disorder
  - B. anxiety
  - C. idiopathic hypersomnia
  - D. irregular sleep-wake rhythm disorder
  - E. obstructive sleep apnea
  
- ▶ 36. In the presence of excessive daytime sleepiness for more than 3 months, which of the following additional features is sufficient for the diagnosis of narcolepsy type 1?
  - A. absence of cataplexy
  - B. CSF hypocretin (orexin) levels of less than 110 pg/mL
  - C. identification of the human leukocyte antigen DQB1\*0602 allele
  - D. response to stimulants
  - E. two sleep-onset rapid eye movement (REM) periods on the multiple sleep latency test

- 37. Which of the following clinical manifestations may be seen during a recurrent bout of Kleine-Levin syndrome?
- A. cataplexy
  - B. convulsive movements
  - C. derealization
  - D. ophthalmoplegia
  - E. sleepwalking
- 38. A 40-year-old man presents to the neurology clinic after experiencing inadequate sleep for more than a year. He states that he usually gets into bed at 10:00 PM, stays awake typically past midnight, and then needs to get up at 6:00 AM for work. He works as a software engineer and states that he feels fatigued at work. He eats a low-fat diet, drinks several cups of coffee at work, and then may work into the evening, when he will switch to diet soda. He exercises daily. He does not watch television in bed. He has tried diphenhydramine for sleep, but feels too groggy the next day. Which of the following is the most likely diagnosis?
- A. adjustment insomnia
  - B. idiopathic insomnia
  - C. inadequate sleep hygiene
  - D. insomnia due to substance abuse
  - E. paradoxical insomnia
- 39. A 12-year-old girl undergoes nocturnal polysomnography due to excessive daytime sleepiness with concern for obstructive sleep apnea. The study reveals an apnea-hypopnea index of 2 per hour with otherwise normal findings. The patient is neurologically and developmentally normal. Her examination reveals a body mass index of 26 kg/m<sup>2</sup> and a normal-appearing midface and oropharynx. Which of the following interventions would be most appropriate based on these results?
- A. rapid maxillary distraction
  - B. tonsillectomy and adenoidectomy
  - C. topical nasal corticosteroids at bedtime
  - D. trial of bilevel positive airway pressure (BiPAP)
  - E. trial of continuous positive airway pressure (CPAP)
- 40. A 7-year-old boy with epilepsy presents to clinic with worsening seizure frequency, increasing irritability, and daytime sleepiness. Despite 12 hours of sleep at night and an hour-long nap most afternoons, he remains sleepy much of the time. His parents note that he snores loudly, and that he has snort arousals at times. He has a normal birth and developmental history. On examination, his body mass index is 15 kg/m<sup>2</sup>. He has large tonsils without exudate and a Friedman grade III tongue position. He appears sleepy, but his neurologic examination is otherwise unremarkable. Overnight polysomnography shows an apnea-hypopnea index of 13 per hour. Which of the following is the most appropriate next step?
- A. counseling for weight loss
  - B. dental evaluation for an oral appliance
  - C. evaluation for tonsillectomy
  - D. evaluation for uvulopalatopharyngoplasty
  - E. repeat polysomnography for continuous positive airway pressure (CPAP) titration



## Postreading Self-Assessment and CME Test—Preferred Responses

Ronnie Bergen, MD; James W. M. Owens Jr, MD, PhD

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the course material. The comments and references included with each question are intended to encourage independent study.

**US Participants:** Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at [aan.com/continuum/cme](http://aan.com/continuum/cme), participants may earn up to 12 AMA PRA Category 1 Credits™ toward SA-CME. US participants have up to 3 years from the date of publication to earn CME credits. No SA-CME will be awarded for this issue after August 31, 2020.

**Canadian Participants:** This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Office of Continuing Medical Education and Professional Development, University of Calgary, on April 1, 2017. Refer to the CME tab on *ContinuumJournal.com* for dates of accreditation. Canadian participants should visit MAINPORT ([www.mainport.org](http://www.mainport.org)) to record learning and outcomes. Canadian participants can claim a maximum of 12 hours (credits are automatically calculated).

- ▶ 1. The preferred response is **E (sleep-related eating disorder)**. This patient's history is most consistent with sleep-related eating disorder. She appears to be partially or fully asleep during the episodes of eating, which would exclude night eating syndrome. A confusional arousal is partial awakening from sleep but does not typically involve ambulation. The behaviors described in this patient seem to be eating related and do not appear to be dream enactment behaviors as would be seen in REM sleep behavior disorder. The excessive eating behavior seen in Kleine-Levin syndrome occurs during wakefulness. For more information, refer to **page 1044** of the *Continuum* article "Non-Rapid Eye Movement Sleep and Overlap Parasomnias."
- ▶ 2. The preferred response is **B (prolonging VNS off time)**. This patient has a history consistent with obstructive sleep apnea emerging in the context of VNS therapy. Given that she is experiencing improvement in her seizure frequency, it is worth modifying stimulation parameters to see if seizure control can be maintained while minimizing apneas. Lowering stimulation frequencies or prolonging off time have been recommended as potentially helpful changes. If this maneuver fails to reduce the apnea-hypopnea index and resolve daytime symptoms, titration with positive airway pressure therapy may be warranted. Tonsillectomy is not indicated in this patient. For more information, refer to **pages 1106 and 1108** of the *Continuum* article "Sleep-Disordered Breathing."
- ▶ 3. The preferred response is **A (lithium)**. This patient has a history consistent with Kleine-Levin syndrome. Lithium and lamotrigine have both demonstrated some efficacy in decreasing the frequency and duration of hypersomnolent episodes. Methylphenidate is a stimulant medication used in patients with excessive daytime sleepiness. Sodium oxybate is used in the treatment of narcolepsy. Trazodone has been used to treat insomnia. For more information, refer to **page 1136** of the *Continuum* article "Sleep-Wake Disorders of Childhood."
- ▶ 4. The preferred response is **B (light)**. Although endogenous circadian rhythms would continue without the influence of exogenous factors, they can be influenced by those factors. For example, meals, exercise, use of medications, and noise can influence normal rhythms. However, presence of light is the strongest exogenous factor influencing circadian rhythms, which makes the application of light a useful treatment for some conditions where circadian rhythms are disrupted. For more information, refer to the **page 1052** of the *Continuum* article "Circadian Rhythm Sleep-Wake Disorders."

- ▶ 5. The preferred response is **C (behavioral insomnia, sleep-onset association type)**. This child appears to have a behavioral type of insomnia, of which the two major types are limit-setting type and sleep-onset association type. Most likely, this is not adjustment insomnia because the child has been in the present setting for a year, and the child is not at a peak age for separation anxiety. Idiopathic insomnia does not imply fixation on an object or identifiable behavior that evokes the insomnia. The limit-setting type of pediatric behavioral insomnia may go together with sleep-onset association type, but not in this case. For more information, refer to **pages 1070–1071** of the *Continuum* article “Chronic Insomnia Disorder.”
- ▶ 6. The preferred response is **B (home sleep apnea testing)**. This patient has a high pretest probability of obstructive sleep apnea given his history, symptoms, and Friedman scale grade. He does not have other conditions that would be a relative contraindication to home sleep apnea testing, such as dementia or congestive heart failure. Therefore, this is the most appropriate initial investigation in this patient. For more information, refer to **pages 978–980** of the *Continuum* article “Diagnostic Approach and Investigation in Sleep Medicine.”
- ▶ 7. The preferred response is **A (at sleep onset)**. Melatonin secretion is influenced by the presence of light. Therefore, its production begins about 2 hours prior to the patient’s normal sleep time and then reaches a peak when sleep begins. Melatonin plateaus during the night and then shows a sharp drop-off at awakening because of the availability of light. Midday would typically show low levels. Following melatonin levels can show the pattern of an individual’s biological night. For more information, refer to the **page 1054** of the *Continuum* article “Circadian Rhythm Sleep-Wake Disorders.”
- ▶ 8. The preferred response is **D (overnight pulse oximetry)**. Overnight pulse oximetry is a useful screening tool for patients with respiratory problems during sleep. If desaturations are found, then overnight polysomnography could be considered. Neuromuscular disease is a relative contraindication for home sleep apnea testing. A multiple sleep latency test could provide objective evidence of somnolence but would not be further interpretable without preceding overnight polysomnography. Serum ferritin would be reasonable to consider if the patient reported other symptoms consistent with restless legs syndrome. For more information, refer to **page 981** of the *Continuum* article “Diagnostic Approach and Investigation in Sleep Medicine.”
- ▶ 9. The preferred response is **C (when sleep-disordered breathing is suspected)**. The elements of conducting a good assessment of insomnia include taking a thorough and chronologic history of the problem, as well as collecting sleep diaries, interviewing bed partners, and assessing for comorbidities (medical, psychological, or substance abuse problems). Polysomnography is not always warranted, particularly if the problem can be assessed using other tools. For more information, refer to **pages 1071–1072** of the *Continuum* article “Chronic Insomnia Disorder.”
- ▶ 10. The preferred response is **C (polysomnography showing REM sleep atonia loss)**. According to the *International Classification of Sleep Disorders, Third Edition*, RBD requires polysomnography to record diagnostic REM sleep atonia loss (ie, to measure muscle activity, usually from the chin and flexor digitorum superficialis muscles) during REM sleep. Questionnaires and historical reports, particularly by a bed partner or other observers of the patient’s sleep, may also be useful for the diagnosis of probable RBD when polysomnography is unavailable or when REM sleep is not recorded during polysomnography. However, dream enactment and vocalizations in sleep are not entirely specific for RBD and can be seen in motor arousals associated with obstructive sleep apnea, in non-REM parasomnias, or even in sleep-related epilepsies. Severe periodic limb movements in sleep might be mistaken for motor activity in RBD, and dementia with sleepwalking or nocturnal wandering may indicate non-REM parasomnia or sundowning behaviors associated with a major cognitive disorder rather than RBD. For more information, refer to **page 1018** and **Table 5-1** of the *Continuum* article “Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias.”
- ▶ 11. The preferred response is **B (decreased sleep efficiency)**. Polysomnography early in the hypersomnolent episode in a patient with Kleine-Levin syndrome typically will reveal poor quality sleep as indicated by decreased sleep efficiency, increased arousals, and decreased slow-wave sleep. There are no significant changes in REM atonia or in periodic limb movements in Kleine-Levin syndrome. For more information, refer to **pages 1035–1036** of the *Continuum* article “Sleep-Wake Disorders of Childhood.”

- ▶ 12. The preferred response is **E (obstructive sleep apnea)**. This patient may have several risk factors for headache, including tobacco use, but his history of headaches that are generally confined to the morning upon awakening and are holocephalic and pressure-like should raise the question of possible sleep apnea. Cluster headaches are typically brief, severe, and unilateral in quality. The absence of papilledema is not supportive of increased intracranial pressure. Exertional headaches should be temporally related to the activity performed, which is not the case here. Hypnic headaches typically awaken the patient after a few hours of sleep and are short lived. For more information, refer to **pages 1120–1121** and **Table 10-2** of the *Continuum* article “Comorbid Sleep Disturbances in Neurologic Disorders.”
  
- ▶ 13. The preferred response is **A (alcohol withdrawal)**. This man appears to be in a confused hallucinatory state consistent with oneiric stupor, the behavioral manifestation of agrypnia excitata. This diagnosis is further supported by the autonomic hyperactivity and dissociation of sleep states. Of the potential causes listed, only alcohol withdrawal is associated with agrypnia excitata. Autoimmune hepatitis and zolpidem use have been associated with sleep-related eating disorder. Corticobasal degeneration can be associated with insomnia but is not known to exhibit agrypnia excitata. While severe depression can be associated with disrupted and fragmented sleep, it would not produce a clinical picture of this severity. For more information, refer to **page 1048** of the *Continuum* article “Non–Rapid Eye Movement Sleep and Overlap Parasomnias.”
  
- ▶ 14. The preferred response is **C (ferritin)**. This patient’s history strongly suggests the diagnosis of restless legs syndrome, and a serum ferritin measurement would therefore be indicated. No reason exists in this patient to suspect renal disease or a neuropathy given her otherwise unremarkable history and her normal neurologic examination. For more information, refer to **pages 982–983** of the *Continuum* article “Diagnostic Approach and Investigation in Sleep Medicine.”
  
- ▶ 15. The preferred response is **A (avoid late-evening napping)**. This individual does not have difficulty with sleep onset but does have difficulty with sleep maintenance. This problem is having an impact on daytime functioning, and, because he works, he does not nap earlier in the day. However, by taking evening naps, although he does not report a problem with sleep onset, excessive sleeping in the evening may be problematic for maintaining sleep at night. Late-evening napping also partially restores the homeostatic drive for sleep and can lead to difficulties with sleep initiation. Ideal naps are usually short (15 to 20 minutes) and are recommended to be taken when the circadian alertness drops around 1:00 PM to 3:00 PM. Early morning caffeine use does not seem to be a problem, whereas watching television in bed might affect sleep onset. Use of a hypnotic may not be indicated as a first step. For more information, refer to **pages 1075–1077** and **Table 8-3** of the *Continuum* article “Chronic Insomnia Disorder.”
  
- ▶ 16. The preferred response is **C (increased EMG activity during REM sleep)**. This patient’s history is strongly suggestive of REM sleep behavior disorder, which is caused by loss of REM sleep–related muscle atonia. Therefore, a clinician would expect to see increased EMG activity during REM sleep. The nonstereotyped nature of the movements as well as the relationship to dream mentation would make epilepsy very unlikely. Nothing in the patient’s history raises suspicion of sleep apnea. Sleep-onset REM periods would be characteristic of narcolepsy and not REM sleep behavior disorder. For more information, refer to **pages 985–986** of the *Continuum* article “Diagnostic Approach and Investigation in Sleep Medicine.”
  
- ▶ 17. The preferred response is **B (excessive daytime sleepiness)**. Excessive daytime sleepiness is the most common presenting symptom in narcolepsy. Sleep paralysis and dream enactment are associated with narcolepsy but are less common. Despite the presence of fragmented nighttime sleep at times, patients with narcolepsy typically report sleep as refreshing. Sleepwalking is a parasomnia seen in non–rapid eye movement (REM) sleep and is rarely associated with narcolepsy. For more information, refer to **pages 990–992** of the *Continuum* article “Narcolepsy and Other Central Hypersomnias.”
  
- ▶ 18. The preferred response is **C (pramipexole)**. Augmentation can make the treatment of RLS complicated and is most likely to be associated with short-acting dopaminergic agents, including pramipexole and ropinirole. Strategies for avoiding or treating augmentation include use of nondopaminergic drugs, long-acting dopaminergic drugs, or opioids. For more information, refer to **pages 1009–1011** and **Table 4-4** of the *Continuum* article “Restless Legs Syndrome and Sleep-Related Movement Disorders.”

- 19. The preferred response is **C (histamine 1 [H<sub>1</sub>] receptor antagonism)**. Doxepin is a tricyclic antidepressant that is approved in very low doses (below any doses typically initiated for depression) for sleep maintenance insomnia and has the advantage of not being a controlled drug. It has an antihistamine effect, which promotes sleep. GABA-A receptor agonists comprise benzodiazepines and nonbenzodiazepines. Hypocretin/orexin receptor antagonists are a new class of drug in which the mechanism of action is essentially to disrupt the wakefulness cycle induced by the hypocretin/orexin-mediated system. Off-label drugs used for sleep, including quetiapine, may work partially by dopamine blocking mechanisms, whereas other off-label antidepressants are primarily norepinephrine and serotonin agonists. For more information, refer to **pages 1084–1085** of the *Continuum* article “Chronic Insomnia Disorder.”
- 20. The preferred response is **D (insufficient sleep for age)**. This 9-year-old patient is getting only 8.5 hours of sleep on weekdays and 10.5 hours of sleep on weekends. This would be insufficient sleep for most school-age children, who need 10 to 11 hours every night. Overall, her sleep hygiene seems adequate, and her history and examination do not suggest a high risk for obstructive sleep apnea, although this must always be kept in mind. She does not have a delayed sleep phase as she can readily fall asleep at 10:00 PM on weeknights. A reasonable approach would be to try sleep extension and then, if this does not result in significantly improved daytime function, to investigate other potential causes. For more information, refer to **pages 1133–1134** and **Table 11-1** of the *Continuum* article “Sleep-Wake Disorders of Childhood.”
- 21. The preferred response is **E (reassure sleep partner)**. In this instance, the patient may be having periodic limb movements of sleep, but there is no impact on sleep quality; therefore, no intervention is needed. For more information, refer to **page 1011** of the *Continuum* article “Restless Legs Syndrome and Sleep-Related Movement Disorders.”
- 22. The preferred response is **E (sleepwalking)**. The clinical features of this patient’s episodes are most consistent with sleepwalking, which is a non-REM parasomnia. The positive family history of similar episodes, her age (10 years being the peak incidence for sleepwalking), and her normal neurodevelopmental examination all support this diagnosis. She has no clear history of dream enactment behaviors. The motoric features of nocturnal frontal lobe epilepsy would likely be more dramatic and bizarre. Agrypnia excitata is excluded by the patient’s normal functioning outside of these episodes. Periodic limb movements of sleep do not result in coordinated ambulation. For more information, refer to **pages 1038–1039** and **Table 6-5** of the *Continuum* article “Non–Rapid Eye Movement Sleep and Overlap Parasomnias.”
- 23. The preferred response is **B (clonazepam)**. This patient’s clinical and polysomnographic findings are consistent with REM sleep behavior disorder (RBD). First-line pharmacologic treatment of RBD symptoms are clonazepam and melatonin at bedtime and are both effective in reducing dream-enacting intensity and frequency. Antidepressants, including tricyclics, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) can induce RBD. For more information, refer to **page 1027** of the *Continuum* article “Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias.”
- 24. The preferred response is **A (autoimmune)**. While genetic factors likely play a large predisposing role in the loss of hypocretin-producing neurons in narcolepsy type 1, evidence from animal studies (in mice) and epidemiologic evidence (eg, discordance in monozygotic twins, association with the influenza A [H1N1] flu pandemic) suggest that the disorder may have an autoimmune basis. For more information, refer to **pages 992–993** of the *Continuum* article “Narcolepsy and Other Central Hypersomnias.”
- 25. The preferred response is **E (sleep terrors)**. The patient’s episodes are most consistent with sleep terrors (previously known as and still more commonly called night terrors), a non-REM parasomnia that is most likely to arise from sleep stage N3, although can also occur in N2 or even N1 sleep. For this reason, non-REM parasomnias such as sleep terrors are more likely to occur in the first part of the night when more N3 sleep occurs. Confusional arousals are another form of non-REM parasomnias, but typically lack the autonomic features found in sleep terrors. Non-REM parasomnias are more likely to occur in the second half of the night given the predominance of this sleep stage during this part of the sleep period. Nightmares are REM parasomnias that most often involve unpleasant or terrifying dream mentation, may involve vocalization, but, instead, most often involve vivid dream recall upon arousal following the event, without amnesia. REM sleep behavior disorder has more variable dream recall and typically involves complex motor behavior that parallels dream content. Panic attacks most often involve a feeling of acute anxiety or doom on awakening, a feeling of palpitations, and do not involve confusion, amnesia, or prominent vocalization on most occasions. Sleep-related temporal lobe seizures are also possible, but often involve motor automatisms and less often have prominent vocalization or autonomic features. For more information, refer to **page 1039** and **Table 6-6** of the *Continuum* article “Non–Rapid Eye Movement Sleep and Overlap Parasomnias.”



- ▶ 26. The preferred response is **A (cognitive-behavioral therapy)**. This girl appears to have a nightmare disorder related to a traumatic experience. The fact that she is fully awake after the nightmare and that she can describe the nightmare in detail is supportive of this diagnosis. Treatment should begin with cognitive-behavioral therapy, which can help the patient to reframe and rescript her dreams. Fluoxetine would tend to suppress rapid eye movement (REM) sleep but is not indicated in this patient without a mood disorder and who would run the risk of REM sleep rebound with vivid dreams once the medication is discontinued. She does not have evidence of a circadian rhythm disorder, for which melatonin could be effective. Zolpidem is not frequently used in children and could worsen the patient's vivid dreams. Scheduled awakening is a technique that can be used with non-REM parasomnias rather than with REM-related phenomena, as this seems to be. For more information, refer to **page 1147** of the *Continuum* article "Sleep-Wake Disorders of Childhood."
- ▶ 27. The preferred response is **B (resolve in 1 to 3 months)**. This patient is exhibiting Cheyne-Stokes respirations, a common respiratory pattern following acute strokes. Most commonly, this pattern resolves within 1 to 3 months. For more information, refer to **pages 1105–1106** of the *Continuum* article "Sleep-Disordered Breathing."
- ▶ 28. The preferred response is **E (treat with continuous positive airway pressure [CPAP] for 1 month and then perform a multiple sleep latency test)**. In a patient with symptoms very suspicious for narcolepsy with cataplexy, a multiple sleep latency test would confirm the diagnosis, but false-positive results can be obtained if sleep apnea is not first adequately treated. The episodes of muscle weakness triggered by emotions suggest cataplexy rather than seizures, so an EEG would not be an appropriate test. Serum ferritin testing would be of no use in this patient without a history suggestive of restless legs syndrome and without periodic limb movements on overnight polysomnography. Treatment with modafinil is not recommended before a firm diagnosis is made. For more information, refer to **pages 979–980** of the *Continuum* article "Diagnostic Approach and Investigation in Sleep Medicine."
- ▶ 29. The preferred response is **A (amygdala)**. The association between cataplexy and activity of the amygdala is suggested by the frequent triggering of cataplectic attacks by strong emotion. This association has been supported by neuropathologic, structural, and neurophysiologic data. For more information, refer to **pages 1094–1096** of the *Continuum* article "Brain Circuitry Controlling Sleep and Wakefulness."
- ▶ 30. The preferred response is **D (stretching exercises)**. Although use of quinine was found to be modestly beneficial for sleep-related cramps, its risks have been felt to outweigh its benefits by the US Food and Drug Administration (FDA). The least risky treatment that has shown some efficacy is the use of calf and leg stretches. For more information, refer to **pages 1011–1013** of the *Continuum* article "Restless Legs Syndrome and Sleep-Related Movement Disorders."
- ▶ 31. The preferred response is **D (light therapy in late afternoon)**. Individuals with advanced sleep-wake phase disorder fall asleep and awaken earlier than desired. Although some role may exist for agents or activities that promote sleep, the most effective therapy for delaying the major sleep phase is light therapy. For more information, refer to the **pages 1057–1058** of the *Continuum* article "Circadian Rhythm Sleep-Wake Disorders."
- ▶ 32. The preferred response is **E (ventrolateral preoptic area of hypothalamus)**. Of the nuclei listed, the ventrolateral preoptic area of the hypothalamus is primarily involved in generating non-REM sleep, while the other nuclei are wakefulness-promoting centers (locus coeruleus, orexinergic neurons of the lateral hypothalamus, dorsal raphe nuclei, and tuberomammillary nucleus). For more information, refer to **pages 960–961** of the *Continuum* article "Brain Circuitry Controlling Sleep and Wakefulness."
- ▶ 33. The preferred response is **B (clonazepam)**. Clonazepam is a first-line pharmacotherapy for non-rapid eye movement (REM) parasomnias once issues of sleep hygiene have been addressed and sleep-disordered breathing or periodic limb movements have been treated, if present. Quetiapine and topiramate can both provoke sleepwalking. Pramipexole can be useful in the management of restless legs syndrome but not sleepwalking. Carbamazepine has been reported useful in treating agrypnia excitata. For more information, refer to **pages 1043–1044** of the *Continuum* article "Non-Rapid Eye Movement Sleep and Overlap Parasomnias."
- ▶ 34. The preferred response is **B (congestive heart failure)**. All the disorders listed are associated with central sleep apnea with a hypercapnic response except for congestive heart failure, which is associated with a hypocapnic response. The hypercapnic disorders are generally related to impaired central drive or to impaired respiratory motor control. The hypocapnia seen with central sleep apneas in congestive heart failure is related to excessive hyperpnea in response to initial hypercapnia caused by apnea. The hyperpnea, in turn, produces hypocarbia. For more information, refer to **page 1104** of the *Continuum* article "Sleep-Disordered Breathing."



- 35. The preferred response is **D (irregular sleep-wake rhythm disorder)**. Patients with irregular sleep-wake rhythm disorder sleep a sufficient amount of time, but at highly irregular intervals, including a shortened nighttime sleep period and multiple prolonged naps during the day. This condition is more common in patients with neurodegenerative disorders, such as dementia, as in this case. For more information, refer to the **page 1060** and **Table 7-4** of the *Continuum* article “Circadian Rhythm Sleep-Wake Disorders.”
- 36. The preferred response is **B (CSF hypocretin (orexin) levels of less than 110 pg/mL)**. The CSF hypocretin level is a reliable biomarker for the diagnosis of narcolepsy type 1. Narcolepsy type 1 may be diagnosed when the CSF hypocretin level is less than 110 pg/mL or when cataplexy is present (while absence of cataplexy is instead seen with narcolepsy type 2). The other listed options could be consistent with a diagnosis of either narcolepsy types 1 or 2, but, of these, only option E is a defining diagnostic feature of narcolepsy type 1 or 2 (ie, which is supported by two or more sleep-onset REM periods on the multiple sleep latency test), and neither of the other options would be considered sufficient for a narcolepsy diagnosis. For example, approximately 25% of individuals in the general population who do not have a sleep disorder carry the human leukocyte antigen allele DQB1\*0602 (which is highly associated, yet nonspecific, for narcolepsy type 1), and other conditions such as circadian disorders, untreated sleep apnea, sedating medications, or recent sleep restriction/deprivation may also produce sleep-onset REM periods on a multiple sleep latency test and may respond to stimulants, at least temporarily, and other clinical events such as syncope, seizures, or functional behaviors may mimic cataplexy. For more information, refer to **page 1000** of the *Continuum* article “Narcolepsy and Other Central Hypersomnias.”
- 37. The preferred response is **C (derealization)**. Kleine-Levin syndrome is more common in boys and presents as recurrent periods of very prolonged sleep associated with behavioral and cognitive impairment and psychiatric manifestations such as derealization, amnesia, confusion, and disorders of perception (eg, hallucinations, delusions). Between episodes, mood, alertness, cognitive function, and behavior are strictly normal. Abnormal movements, cranial neuropathies, or non-rapid eye movement (REM) parasomnias are not typical of this disorder. For more information, refer to **pages 1000–1001** of the *Continuum* article “Narcolepsy and Other Central Hypersomnias.”
- 38. The preferred response is **C (inadequate sleep hygiene)**. In determining this patient’s diagnosis, consideration should be given to his use of caffeine, which sometimes extends into the evening, interfering with his ability to fall asleep. A modification of this behavior may effectively improve his symptoms. For more information, refer to **pages 1069–1070** of the *Continuum* article “Chronic Insomnia Disorder.”
- 39. The preferred response is **C (topical nasal corticosteroids at bedtime)**. This patient has an apnea-hypopnea index of 2 per hour, indicative of mild OSA. The most appropriate treatment is topical nasal corticosteroids at bedtime. There is no indication to pursue a tonsillectomy and adenoidectomy with this mild degree of OSA, particularly given the patient’s normal-appearing oropharynx. The same findings would argue against rapid maxillary distraction. BiPAP and CPAP would be reserved for moderate to severe OSA. For more information, refer to **page 1142** of the *Continuum* article “Sleep-Wake Disorders of Childhood.”
- 40. The preferred response is **C (evaluation for tonsillectomy)**. This boy has a history and examination concerning for obstructive sleep apnea, which is confirmed by overnight polysomnography. Given his normal body mass index and crowded posterior oropharynx, evaluation for a tonsillectomy and adenoidectomy would be the best first step. Should this prove ineffective, then CPAP could be considered. The role of uvulopalatopharyngoplasty is unclear in adults and is not established in children. For more information, refer to **page 1108** of the *Continuum* article “Sleep-Disordered Breathing.”

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**Relationship Disclosure:**

Dr St. Louis serves on the editorial boards of *Continuum* and the Sleep and Chronobiology section of *Frontiers in Neurology*. Dr St. Louis has received personal compensation for serving as a consultant in clinical trial design for Axovant Sciences Ltd; for serving on the data safety monitoring board of Inspire Medical Systems, Inc; and has received research/grant support from Axovant Sciences Ltd; Mayo Clinic Center for Clinical and Translational Science; the Michael J. Fox Foundation; the National Institutes of Health/National Heart, Lung, and Blood Institute; and Sunovion Pharmaceuticals Inc. Dr St. Louis has received royalties from Wiley-Blackwell for the book, *Epilepsy and the Interictal State: Co-morbidities and Quality of Life*.

**Unlabeled Use of Products/Investigational Use Disclosure:**

Dr St. Louis discusses the off-label use of clonazepam and melatonin for the treatment of rapid eye movement sleep behavior disorder.

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## Patient Management Problem

Erik K. St. Louis, MD, MS, FAAN, FAASM

The following Patient Management Problem was chosen to reinforce the subject matter presented in the issue. It emphasizes decisions facing the practicing physician. As you read through the case you will be asked to complete 12 questions regarding history, examination, diagnostic evaluation, therapy, and management. For each item, select the single best response.

To obtain CME credits for this activity, subscribers must complete this Patient Management Problem online at [aan.com/continuum/cme](http://aan.com/continuum/cme). A tally sheet is provided with this issue to allow the option of marking answers before entering them online. A faxable scorecard is available only upon request to subscribers who do not have computer access or to nonsubscribers who have purchased single back issues (send an email to [ContinuumCME@aan.com](mailto:ContinuumCME@aan.com)).

**US Participants:** Upon completion of the Patient Management Problem, US participants may earn up to 2 *AMA PRA Category 1 Credits*<sup>™</sup>. US participants have up to 3 years from the date of publication to earn CME credits. No CME will be awarded for this issue after August 31, 2020.

**Canadian Participants:** This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, and approved by the Office of Continuing Medical Education and Professional Development, University of Calgary, on April 1, 2017. Refer to the CME tab on *ContinuumJournal.com* for dates of accreditation. Canadian participants should visit MAINPORT ([www.mainport.org](http://www.mainport.org)) to record learning and outcomes. Canadian participants can claim a maximum of 2 hours (credits are automatically calculated).

### LEARNING OBJECTIVES

Upon completion of this activity, the participant will be able to:

- Distinguish symptoms of sleepiness from fatigue and nonspecific tiredness
- Differentiate and categorize multiple concurrent sleep comorbidities by a problem-oriented approach
- Direct an appropriately sequenced evaluation and treatment strategy for patients with multiple sleep disturbances
- Understand the relationship between sleep comorbidities and neuromuscular disorders
- Select between appropriate psychostimulant and wake-promoting treatment options for narcolepsy and related primary central nervous system hypersomnias
- Discuss the diagnosis and management of core sleep neurology disorders including narcolepsy, restless legs syndrome, and rapid eye movement sleep behavior disorder

## Case

A 62-year-old woman is seen for reported tiredness that she has experienced since childhood. She recalls that even as a child, she had an intense desire to go to bed at night and, unlike her siblings, could never stay up at times of parties; she would instead go to sleep on the bathroom floor in the most quiet and remote location in their home until her parents would put her to bed. She also recalls having regularly fallen asleep in the classroom during her school and collegiate years and notes episodic involuntary sleepiness while driving with a few near-miss incidents, including highway midline crossings or hitting the highway rumble strips after nodding off at the wheel. She always feels tired during the daytime despite regularly obtaining 8 to 9 hours of sleep each night. Her bedtime is at approximately 9:00 PM to 10:00 PM, and she falls asleep quickly within about 5 minutes and sleeps well throughout the night without intervening awakenings. She arises without an alarm each morning at about 6:00 AM to 6:30 AM, feeling well refreshed, but becomes drowsy again within hours of awakening and requires at least one or two 10-minute naps daily, which are consistently highly refreshing in quality.

For the last 4 to 5 years, the patient has also noted a quality of enduring tiredness with poor energy and a lack of desire or motivation to pursue activities she previously enjoyed, such as hiking or going for evening walks with her husband after work. She continues to function well during her work hours as a store clerk. Most days she remains alert and able to work provided she remains on her feet, although on each of her 15-minute breaks per 4-hour work period, she returns to her car in the parking lot to nap.

She has recently also been undergoing systemic evaluation for generalized weakness and gastrointestinal and endocrine disturbances. Her past medical history is remarkable only for treated hypertension and gastroesophageal reflux, and her only medications are enalapril 5 mg/d and omeprazole 40 mg/d.

Neurologic examination demonstrates mild proximal weakness involving her deltoids, triceps, iliopsoas, and hamstring muscles, with normal cervical flexion/extension strength and muscle tone, absence of fasciculations, and a normal sensory examination. Muscle stretch reflexes are present but slightly reduced throughout, and plantar responses are flexor.

- 1. Which of the following bedside questionnaires would provide the best insight into the patient's daytime tiredness?
- A. Daytime Sleepiness Scale
  - B. Epworth Sleepiness Scale
  - C. Faces Sleepiness Scale
  - D. Karolinska Sleepiness Scale
  - E. Stanford Sleepiness Scale

The patient's Epworth Sleepiness Scale score is 16, indicating likely excessive daytime sleepiness. Additional collateral history is taken from the patient's husband. He states that she has been snoring for the last 5 years, and it is occasionally disruptive. When she sleeps on her back, he needs to poke or nudge her. Rarely, he has to leave the bedroom, and on those occasions, he can still hear her snore in the neighboring bedroom with both doors shut. She occasionally pauses while breathing during sleep, and every few months she snores herself awake or awakens with a gasping or choking sensation. She regularly awakens in the morning with an extremely dry mouth and occasionally also notes a sore throat.

On examination, her Friedman palate position is grade IV, neck circumference is 41 cm, blood pressure is 142/92 mm Hg, pulse rate is 72 beats/min, and her body mass index is 27 kg/m<sup>2</sup>. The remainder of her general physical examination is normal.

- 2. Which of this patient's historical symptoms or physical examination signs is most indicative of a high pretest probability of obstructive sleep apnea (OSA)?
- A. excessive daytime sleepiness
  - B. loud disruptive snoring
  - C. neck circumference
  - D. obesity
  - E. observed breathing pauses

Polysomnography is performed to determine whether significant OSA or periodic limb movement disorder may be present or if evidence exists for central hypersomnolence. The polysomnogram demonstrates an apnea-hypopnea index of 17 per hour, with the predominant event type shown in **PMP Figure 1**.



**PMP FIGURE 1**

Diagnostic polysomnogram showing a 2-minute epoch. This example shows repeated associated electroencephalographic arousals (channels 3–5), cessation of airflow in the thermistor and nasal pressure sensor (channels 9–10), oxyhemoglobin desaturation in the pulse oximeter (channel 12), and continued respiratory effort with abdominal paradox in the plethysmography bands (channels 14–15).

- 3. Which of the following diagnoses is supported by the polysomnogram epoch shown in **PMP Figure 1**?
- A. Cheyne-Stokes respirations
  - B. idiopathic central sleep apnea
  - C. OSA
  - D. sleep-related hypoventilation
  - E. upper airway resistance syndrome

During diagnostic polysomnography, mean oxyhemoglobin saturation was 93% (nadir of 84%), and the periodic limb movement index was 98 per hour, with a periodic limb movement arousal index of 22 per hour. The initial rapid eye movement (REM) latency was 52 minutes (within laboratory normative standards for age). While the patient had denied substantial symptoms of restless legs on initial intake history, further history taking is prompted by revelation of frequent periodic leg movements of sleep with heightened movement arousal during polysomnography. She noted intense restlessness in her legs during the night of polysomnogram recording and, in retrospect, realizes that she experiences similar habitual restless legs symptoms about one night every 1 to 2 weeks, during which she feels an uncomfortable aching sensation in both legs, primarily below knee level, with an urge to move that leads her to get up and walk for a few minutes before bedtime to seek relief. However, the symptoms rarely bother her substantially or interfere with her sleep, and her husband is not bothered by her legs moving during sleep, although he does report that she occasionally has notably frequent recurring leg or arm movements during sleep that do not seem to awaken her.

She is counseled about treatment options for her moderately severe OSA and the health implications of a higher associated risk of adverse cardiovascular outcomes and accepts a trial of nasal continuous positive airway pressure (CPAP). She is also diagnosed with restless legs syndrome (RLS).

- 4. Which of the following serum tests should be considered in view of her RLS symptoms?
  - A. ferritin
  - B. magnesium
  - C. potassium
  - D. thyroid-stimulating hormone
  - E. vitamin B<sub>12</sub>
- 5. Which of the following medications is most likely to be associated with iron deficiency?
  - A. octreotide
  - B. ofloxacin
  - C. olmesartan
  - D. omeprazole
  - E. ondansetron

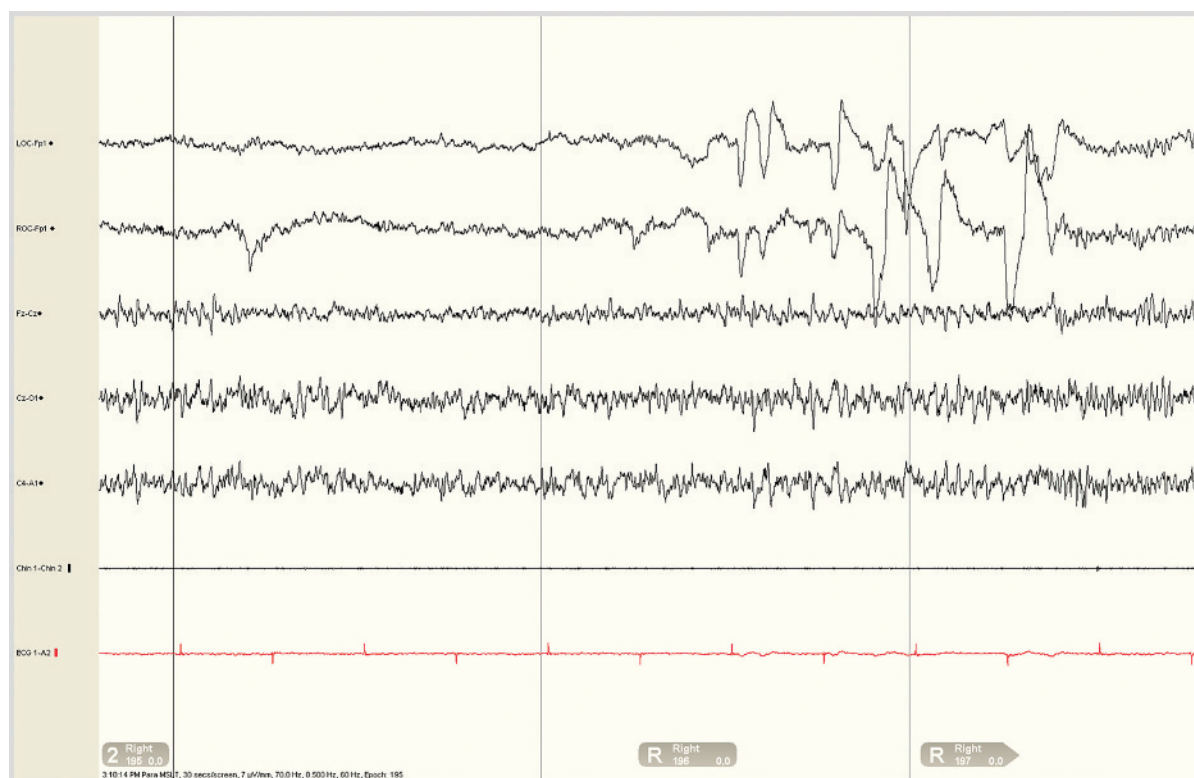
The patient's serum ferritin is 8 ng/mL. She begins iron replacement therapy with ferrous fumarate 65 mg 3 times daily 1 hour before meals. She also had been receiving omeprazole for comorbid gastroesophageal reflux and began that drug about 3 years prior to onset of habitual RLS symptoms, and this was discontinued. In follow-up 2 months later, the patient states that she is tolerating nasal CPAP therapy well using a nasal pillow interface. Review of a compliance report downloaded from her CPAP device demonstrates 92% of nights with 4 hours or greater use for an average of 8 hours and 32 minutes. The 95th percentile CPAP pressure was 7.6 cm on her auto-titrating CPAP device, which had been set spanning the range of 5 cm H<sub>2</sub>O to 15 cm H<sub>2</sub>O. Her RLS symptoms have also essentially resolved.

She feels that her sleep quality has subjectively improved and is enriched. She reports that she can now remember dreams, which are sometimes vivid, for the first time in years. However, she reports no change in the degree of her daytime sleepiness, and a repeat Epworth Sleepiness Scale score was again elevated at 14, with a tendency to nap readily and doze whenever circumstances permit. No symptoms of cataplexy, hypnagogic hallucinations, or sleep paralysis are present.



- 6. Which of the following additional diagnostic evaluations would be most appropriate in evaluating the patient's symptoms of hypersomnolence?
- A. home overnight oximetry
  - B. home sleep testing
  - C. maintenance of wakefulness test
  - D. multiple sleep latency test (MSLT)
  - E. polysomnography

It is verified that the patient is not receiving any sedating medications or antidepressants. She is instructed to continue with CPAP therapy regularly, to continue sleeping at least 8 to 9 hours or longer each night, and to refrain from caffeine use 1 week prior to testing. Repeat polysomnography is also performed on the night prior to MSLT to confirm treatment adequacy for OSA and sleep-fragmenting periodic limb movements. This polysomnogram demonstrates reduced frequency of periodic leg movements of sleep at 18 per hour, with a periodic limb movement arousal index of 2 per hour. During this second polysomnogram, a full CPAP trial is performed, and CPAP titration is found effective at 8 cm H<sub>2</sub>O, her usual recent home treatment pressure. The following day, MSLT is performed with nap opportunities at 9:00 AM, 11:00 AM, 1:00 PM, and 3:00 PM. An example 30-second epoch from the patient's first nap is shown in **PMP Figure 2**.



**PMP FIGURE 2**

Multiple sleep latency test showing a 30-second epoch. This example shows eye movements in the electrooculogram (channels 1–2), mixed-frequency EEG activity with saw-tooth waveforms (channels 3–5), and submental (chin) EMG atonia (channel 6).

► 7. Which of the following sleep stages is shown in the MSLT example in **PMP Figure 2**?

- A. REM sleep
- B. sleep stage N1
- C. sleep stage N2
- D. sleep stage N3
- E. wakefulness

During the MSLT, the patient falls asleep rapidly during each of the four naps, with individual sleep latencies of 2.5, 1.5, 3.0, and 4.0 minutes, yielding a mean sleep latency of 2.8 minutes. There are three sleep-onset REM periods (0 or 1 being normal). The MSLT findings of a short sleep latency (fewer than 8.0 minutes) and two or more sleep-onset REM periods are supportive of a clinical diagnosis of narcolepsy type 2 given that she does not experience cataplexy. She has no history of hypnagogic hallucinations or sleep paralysis.

► 8. Which of the following psychostimulant/wake-promoting agents is the best choice for the initial treatment of hypersomnia in this patient?

- A. bupropion
- B. lisdexamfetamine
- C. methamphetamine
- D. methylphenidate
- E. modafinil

The patient is started on modafinil with titration to 400 mg each morning and experiences markedly improved alertness. With combined CPAP, iron replacement, and stimulant therapy, alertness is satisfactory, and she no longer dozes as often, remains alert while driving, and reports an Epworth Sleepiness Scale score of just 10 at her 3-month follow-up. However, her symptoms of fatigue persist, and her Fatigue Severity Scale rating is 54 (score is elevated with a cutoff of 39).

Concomitant to her sleep workup, she also notes increased muscle aching and worsening weakness that she has experienced over the last year prior to presentation. While having some degree of lifelong weakness, she also began noting more recent difficulties rising from a squatting position, and she notes more recent problems climbing stairs.

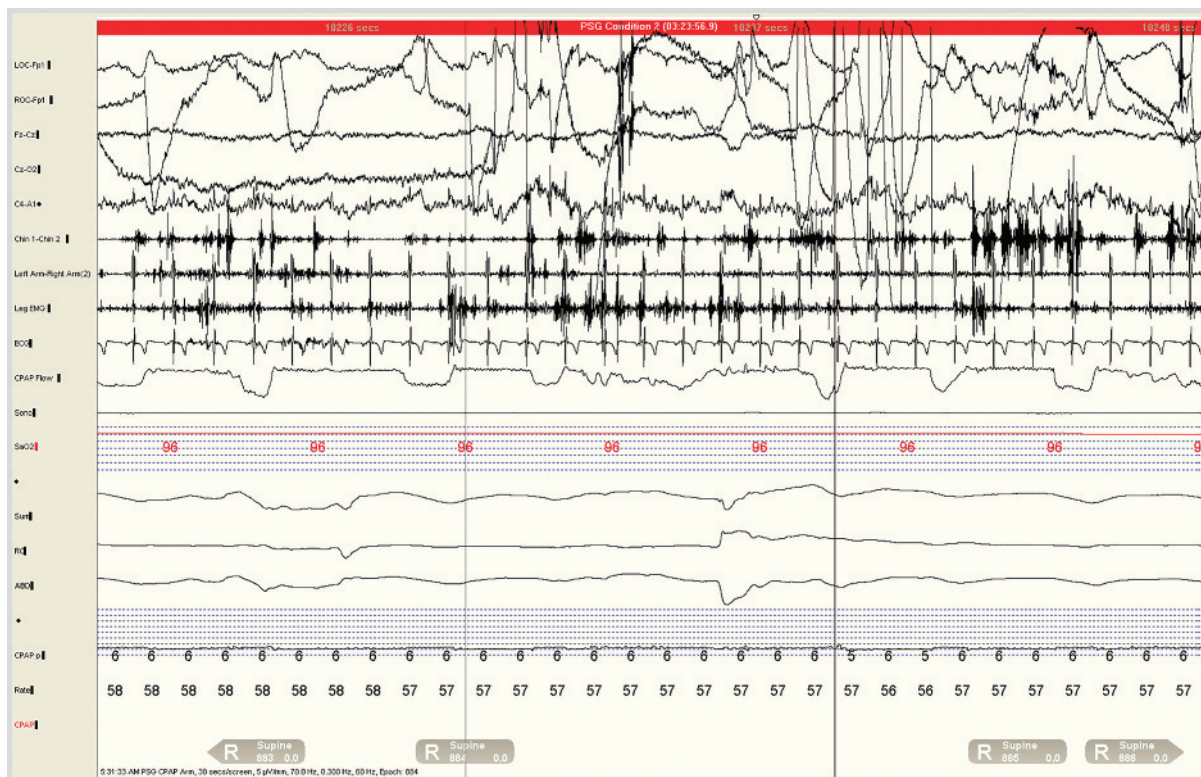
EMG demonstrates low-amplitude compound muscle action potentials (CMAPs), abnormal spontaneous activity with fibrillation potentials and myotonic discharges, and myopathic features of rapid recruitment of short duration and small motor unit potentials in proximal muscles. She notes some mild shortness of breath on exertion, but no orthopnea or paroxysmal nocturnal dyspnea. Pulmonary functions show a mildly reduced vital capacity of 2.16 cm<sup>3</sup>, with reduced maximal inspiratory and expiratory pressures between 36% and 60% of expected values. Arterial blood gas confirmed normocapnia with P<sub>a</sub>CO<sub>2</sub> of 38 torr.

► 9. Considering this patient's mild proximal muscle weakness, myalgias, and sleep disturbances, which of the following underlying associated myopathies is the most likely diagnosis?

- A. Duchenne muscular dystrophy
- B. facioscapulohumeral muscular dystrophy
- C. inclusion body myositis
- D. myotonic dystrophy type 1
- E. myotonic dystrophy type 2

The gene test for myotonic dystrophy type 2 is positive with 6600 CCTG repeats, and she is diagnosed with myotonic dystrophy type 2. For the next year, she does well on a combination of CPAP therapy, iron replacement, and modafinil and reports an improved level of sleepiness of only 8 on the Epworth Sleepiness Scale. At 1-year follow-up, additional collateral history from her husband indicates that since her last visit, she has experienced the onset of new peculiar behaviors during sleep, involving complex motor behaviors that usually occur in the second half of the night. She frequently vocalizes and has either knitting-type movements of the hands (which is one of her daytime hobbies) or, on some occasions, flailing or punching arm movements paralleling recalled dream mentation of being chased by a bear or persons.

Evolution of the new nocturnal behaviors prompt further review of her previous polysomnogram, and a representative epoch is shown in **PMP Figure 3**.



**PMP Figure 3** Polysomnogram showing a 30-second epoch. This epoch shows excessive phasic muscle activity bursts in the chin, arm, and leg EMG (channels 6–8). Characteristic rapid eye movement (REM) sleep features include rapid eye movements in the electrooculogram (channels 1–2) and relatively desynchronized mixed-frequency EEG activity (channels 3–5).

- 10. Which of the following findings is evident in the polysomnogram REM sleep epoch shown in **PMP Figure 3**?
- A. abnormal eye movements
  - B. alternating leg movement activation
  - C. atonia loss
  - D. normal atonia
  - E. periodic leg movements

The patient is diagnosed with REM sleep behavior disorder (RBD) and is prescribed clonazepam 0.5 mg nightly at bedtime. At 2-month follow-up, her husband reports that the patient continues to manifest violent dream enactment behaviors at least twice weekly, with punching, kicking, and screaming paralleling nightmarish dream content. Despite further titration of clonazepam to 2.0 mg nightly, behaviors continue, and she has had one fall from bed, which bruised her arm, and has punched her husband on another occasion as she dreamt she was being attacked by a bear. She also reported worsened daytime sedation and mild unsteadiness.

- 11. Which of the following treatments should be considered in view of the patient's continued dream enactment?
- A. carbamazepine
  - B. donepezil
  - C. melatonin
  - D. pramipexole
  - E. ramelteon

Since clonazepam had been ineffective at doses of 2.0 mg nightly, the patient is started on melatonin 3 mg nightly, but because of continued sporadic violent behaviors at 6-month follow-up, melatonin is further titrated to 6 mg nightly, with a substantial decrease in the frequency of her dream enactment behaviors. Further longitudinal follow-up annually over 5 years shows no further evolution of new neurologic symptoms or signs.

- 12. This patient's parasomnia diagnosis suggests heightened risk for future development of which of the following neurologic diagnoses?
- A. IgLON5 autoimmunity
  - B. multiple sclerosis
  - C. Parkinson disease
  - D. pontine astrocytoma
  - E. Wilson disease

This case exemplifies several important principles in sleep neurology practice. First, sleepiness and fatigue are common symptoms in patients with neurologic disorders, and the Epworth Sleepiness Scale is a helpful bedside tool to enable recognition of significant symptoms of daytime sleepiness that may signify the need to consider whether an underlying primary sleep disorder exists. Second, sleep medicine patients frequently have multiple overlapping symptoms of sleep disturbance, requiring a logical, sequential approach to effectively distinguish different sleep disorders that require specific therapeutic approaches. In this patient, the initial approach was to distinguish two diagnoses impacting sleep quality using polysomnography, OSA and RLS, requiring treatment by nasal CPAP and iron replacement therapy. Second, after symptoms of sleepiness persisted, an underlying narcolepsy type 2 diagnosis, suggested by her history of lifelong sleepiness, was supported by MSLT evaluation. Third, continued symptoms of daytime tiredness persisted following combined CPAP, iron, and stimulant therapy with modafinil, suggesting prominent fatigue accompanying another neurologic disorder causing proximal weakness, which proved to be myotonic dystrophy type 2. Last, the importance of longitudinal follow-up was demonstrated by evolution of dream enactment behavior and subsequent diagnosis of RBD, which necessitates further longitudinal follow-up to guide treatment for injury prevention and enable monitoring and treatment for symptoms and signs of synucleinopathy. Sleep neurology includes a myriad of fascinating diagnostic considerations, requiring broad interdisciplinary clinical, neurophysiology, and pharmacologic management expertise, and the possibility of improving functioning and quality of life for our patients.<sup>1</sup>

1. St Louis EK. Key sleep neurologic disorders: narcolepsy, restless legs syndrome/Willis-Ekbom disease, and REM sleep behavior disorder. *Neurol Clin Pract* 2014;4(1):16–25. doi:10.1212/01.CPJ.0000442523.60659.02.

**ACKNOWLEDGMENT**

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# Patient Management Problem—Preferred Responses

Erik K. St Louis, MD, MS, FAAN, FAASM

Following are the preferred responses for the Patient Management Problem in this *Continuum* issue. The case, questions, and answer options are repeated, and the preferred response is given, followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the material. The comment and references included with each question are intended to encourage independent study.

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## Relationship Disclosure:

Dr St. Louis serves on the editorial boards of *Continuum* and the Sleep and Chronobiology section of *Frontiers in Neurology*. Dr St. Louis has received personal compensation for serving as a consultant in clinical trial design for Axovant Sciences Ltd; for serving on the data safety monitoring board of Inspire Medical Systems, Inc; and has received research/grant support from Axovant Sciences Ltd; Mayo Clinic Center for Clinical and Translational Science; the Michael J. Fox Foundation; the National Institutes of Health/National Heart, Lung, and Blood Institute; and Sunovion Pharmaceuticals Inc. Dr St. Louis has received royalties from Wiley-Blackwell for the book, *Epilepsy and the Interictal State: Co-morbidities and Quality of Life*.

## Unlabeled Use of Products/Investigational Use Disclosure:

Dr St. Louis discusses the off-label use of clonazepam and melatonin for the treatment of rapid eye movement sleep behavior disorder.

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## LEARNING OBJECTIVES

Upon completion of this activity, the participant will be able to:

- Distinguish symptoms of sleepiness from fatigue and nonspecific tiredness
- Differentiate and categorize multiple concurrent sleep comorbidities by a problem-oriented approach
- Direct an appropriately sequenced evaluation and treatment strategy for patients with multiple sleep disturbances
- Understand the relationship between sleep comorbidities and neuromuscular disorders
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- Discuss the diagnosis and management of core sleep neurology disorders including narcolepsy, restless legs syndrome, and rapid eye movement sleep behavior disorder



Supplemental digital content: Direct URL citations appear in the printed text and are included in the HTML, PDF, and app versions of this article.

## Case

A 62-year-old woman is seen for reported tiredness that she has experienced since childhood. She recalls that even as a child, she had an intense desire to go to bed at night and, unlike her siblings, could never stay up at times of parties; she would instead go to sleep on the bathroom floor in the most quiet and remote location in their home until her parents would put her to bed. She also recalls having regularly fallen asleep in the classroom during her school and collegiate years and notes episodic involuntary sleepiness while driving with a few near-miss incidents, including highway midline crossings or hitting the highway rumble strips after nodding off at the wheel. She always feels tired during the daytime despite regularly obtaining 8 to 9 hours of sleep each night. Her bedtime is at approximately 9:00 PM to 10:00 PM, and she falls asleep quickly within about 5 minutes and sleeps well throughout the night without intervening awakenings. She arises without an alarm each morning at about 6:00 AM to 6:30 AM, feeling well refreshed, but becomes drowsy again within hours of awakening and requires at least one or two 10-minute naps daily, which are consistently highly refreshing in quality.

For the last 4 to 5 years, the patient has also noted a quality of enduring tiredness with poor energy and a lack of desire or motivation to pursue activities she previously enjoyed, such as hiking or going for evening walks with her husband after work. She continues to function well during her work hours as a store clerk. Most days she remains alert and able to work provided she remains on her feet, although on each of her 15-minute breaks per 4-hour work period, she returns to her car in the parking lot to nap.

She has recently also been undergoing systemic evaluation for generalized weakness and gastrointestinal and endocrine disturbances. Her past medical history is remarkable only for treated hypertension and gastroesophageal reflux, and her only medications are enalapril 5 mg/d and omeprazole 40 mg/d.

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- 1. Which of the following bedside questionnaires would provide the best insight into the patient's daytime tiredness?
- A. Daytime Sleepiness Scale
  - B. Epworth Sleepiness Scale
  - C. Faces Sleepiness Scale
  - D. Karolinska Sleepiness Scale
  - E. Stanford Sleepiness Scale

The preferred response is **B (Epworth Sleepiness Scale)**. This patient presents with a lifelong history of excessive daytime sleepiness as well as superimposed symptoms that have more recently evolved, such as fatigue despite adequate quantity and quality of nighttime sleep. She provides a clear-cut history of sleepiness, manifested by her tendency to doze in permissive situations. Yet, she also has more recent-onset fatigue symptoms, characterized by her poor energy level for completing usual activities, and has a more physical, pervasive sense of tiredness that is less specific for sleep disorders or disturbances, since fatigue may also accompany several medical, psychiatric, and neurologic disorders.

The Epworth Sleepiness Scale (**Supplemental Digital Content Appendix**, [links.lww.com/CONT/A222](https://links.lww.com/CONT/A222)) provides insight into habitual daytime sleepiness by posing eight standard questions about the patient's recent likelihood to doze in various permissive daytime settings, such as sitting and reading, watching television, sitting quietly after lunch, lying down in the afternoon, traveling as a passenger in a car, and sitting quietly for a few minutes while stopped in traffic.<sup>1</sup> For each item, the patient self-rates his or her likelihood of dozing in each setting, with a score ranging from 0 (no chance of dozing), 1 (mild chance of dozing), 2 (moderate chance of dozing), or 3 (high chance of dozing), and the scores for each question are added for a total score. Scores of more than 10 indicate the likelihood of excessive daytime sleepiness.

The Epworth Sleepiness Scale is a standard intake questionnaire instrument used in most clinical sleep medicine practices worldwide. The Epworth Sleepiness Scale is a quick, efficient, and convenient screening instrument for sleepiness, typically completed by the patient in 5 minutes or fewer while waiting for their

appointment in the lobby or during the office visit. While not specific for the cause of sleepiness since the Epworth Sleepiness Scale score is elevated in a variety of patients having different causes of sleepiness,<sup>2</sup> the scale is quite helpful in distinguishing the cardinal symptom of excessive daytime sleepiness from the less specific symptom of fatigue. Frequently, overlap exists between sleepiness and fatigue, although sleepiness is more specific for the likelihood of an underlying primary sleep disorder. Use of the Epworth Sleepiness Scale can therefore be helpful in screening for an underlying primary sleep disorder, prompting additional clinical history and indicating the potential usefulness of consulting a sleep medicine physician and considering additional appropriate evaluation (eg, screening for sleep-disordered breathing with polysomnography or home sleep testing in the setting of a patient with a high likelihood of at least moderate-severity obstructive sleep apnea [OSA]).

1. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540–545.

2. Johns MW. Sleepiness in different situations measured by the Epworth sleepiness scale. *Sleep* 1994;17(8):703–710.

The patient's Epworth Sleepiness Scale score is 16, indicating likely excessive daytime sleepiness. Additional collateral history is taken from the patient's husband. He states that she has been snoring for the last 5 years, and it is occasionally disruptive. When she sleeps on her back, he needs to poke or nudge her. Rarely, he has to leave the bedroom, and on those occasions, he can still hear her snore in the neighboring bedroom with both doors shut. She occasionally pauses while breathing during sleep, and every few months she snores herself awake or awakens with a gasping or choking sensation. She regularly awakens in the morning with an extremely dry mouth and occasionally also notes a sore throat.

On examination, her Friedman palate position is grade IV, neck circumference is 41 cm, blood pressure is 142/92 mm Hg, pulse rate is 72 beats/min, and her body mass index is 27 kg/m<sup>2</sup>. The remainder of her general physical examination is normal.

- 2. Which of this patient's historical symptoms or physical examination signs is most indicative of a high pretest probability of obstructive sleep apnea (OSA)?
- A. excessive daytime sleepiness
  - B. loud disruptive snoring
  - C. neck circumference
  - D. obesity
  - E. observed breathing pauses

The preferred response is **C (neck circumference)**. Each of the symptoms and physical signs may increase the likelihood of an OSA diagnosis; yet, of these, the best response is neck circumference. Thickened neck circumference is a marker of central obesity, which has a strong association with sleep apnea and, along with older age and hypertension history, appears to be an independent predictor for an OSA diagnosis.<sup>1</sup> A neck circumference of more than 40 cm is a predictive feature for an OSA diagnosis and is part of the STOP-BANG model (snoring, tiredness, observed breathing pauses, blood pressure too high [hypertension diagnosis], body mass index of more than 35 kg/m<sup>2</sup>, age older than 50 years, neck circumference of more than 40 cm, gender is male). A STOP-BANG score of 3 or more is 93% to 100% sensitive for a moderate or severe OSA diagnosis confirmed by the gold standard of polysomnography. This patient's STOP-BANG score is 6 (out of 7 possible in women and 8 in men, resulting from the sum of positively scored points for loud disruptive snoring, tiredness [sleepiness and fatigue], observed breathing pauses, blood pressure too high [hypertension diagnosis], age older than 50 years, and neck circumference greater than 40 cm [41 cm], while obese body mass index and male gender are absent), which represents a high risk for moderate or severe OSA.<sup>2</sup> The other symptoms are additionally suggestive of a substantial likelihood of clinically significant sleep-disordered breathing.

1. Kim SE, Park BS, Park SH, et al. Predictors for presence and severity of obstructive sleep apnea in snoring patients: significance of neck circumference. *J Sleep Med* 2015;12(2):34–38. doi:10.13078/jsm.15007.

2. Chung F, Abdullah HR, Liao P. STOP-Bang Questionnaire: a practical approach to screen for obstructive sleep apnea. *Chest* 2016;149(3):631–638. doi:10.1378/chest.15-0903.

Polysomnography is performed to determine whether significant OSA or periodic limb movement disorder may be present or if evidence exists for central hypersomnolence. The polysomnogram demonstrates an apnea-hypopnea index of 17 per hour, with the predominant event type shown in **PMP Figure 1**.



**PMP FIGURE 1**

Diagnostic polysomnogram showing a 2-minute epoch. This example shows repeated associated electroencephalographic arousals (channels 3–5), cessation of airflow in the thermistor and nasal pressure sensor (channels 9–10), oxyhemoglobin desaturation in the pulse oximeter (channel 12), and continued respiratory effort with abdominal paradox in the plethysmography bands (channels 14–15).

► 3. Which of the following diagnoses is supported by the polysomnogram epoch shown in **PMP Figure 1**?

- A. Cheyne-Stokes respirations
- B. idiopathic central sleep apnea
- C. OSA
- D. sleep-related hypoventilation
- E. upper airway resistance syndrome

The preferred response is **C (OSA)**. The event type shown in **PMP Figure 1** is a clear obstructive apnea since there is cessation of oronasal airflow with continued breathing effort and abdominal paradox for greater than 10 seconds in duration.<sup>1</sup> Upper airway resistance syndrome is a mild variant of OSA characterized by frequent respiratory effort–related arousals, which are caused by increased effort or work of breathing yet occur without substantial oxyhemoglobin desaturation. Central sleep apnea involves cessation of both airflow and respiratory effort, and Cheyne-Stokes respirations are a specific type of central sleep apnea with a periodic breathing pattern involving phasic periods of apnea and periods of hyperpnea with a full cycle length near 40 seconds in duration.<sup>2</sup>

1. Berry RB, Brooks R, Gamaldo CE, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Version 2.2. Darien, IL: American Academy of Sleep Medicine, 2015.

2. Foldvary-Schaefer NR, Waters TE. Sleep-disordered breathing. *Continuum (Minneapolis)* 2017;23(4 Sleep Neurology):1093–1116.



During diagnostic polysomnography, mean oxyhemoglobin saturation was 93% (nadir of 84%), and the periodic limb movement index was 98 per hour, with a periodic limb movement arousal index of 22 per hour. The initial rapid eye movement (REM) latency was 52 minutes (within laboratory normative standards for age). While the patient had denied substantial symptoms of restless legs on initial intake history, further history taking is prompted by revelation of frequent periodic leg movements of sleep with heightened movement arousal during polysomnography. She noted intense restlessness in her legs during the night of polysomnogram recording and, in retrospect, realizes that she experiences similar habitual restless legs symptoms about one night every 1 to 2 weeks, during which she feels an uncomfortable aching sensation in both legs, primarily below knee level, with an urge to move that leads her to get up and walk for a few minutes before bedtime to seek relief. However, the symptoms rarely bother her substantially or interfere with her sleep, and her husband is not bothered by her legs moving during sleep, although he does report that she occasionally has notably frequent recurring leg or arm movements during sleep that do not seem to awaken her.

She is counseled about treatment options for her moderately severe OSA and the health implications of a higher associated risk of adverse cardiovascular outcomes and accepts a trial of nasal continuous positive airway pressure (CPAP). She is also diagnosed with restless legs syndrome (RLS).

► 4. Which of the following serum tests should be considered in view of her RLS symptoms?

- A. ferritin
- B. magnesium
- C. potassium
- D. thyroid-stimulating hormone
- E. vitamin B<sub>12</sub>

The preferred response is **A (ferritin)**. In addition to OSA, which could account for symptoms of sleepiness or fatigue alone, the patient also manifests frequent periodic leg movements of sleep with heightened movement arousal tendency during polysomnography. While periodic leg movements are a nonspecific finding in adult polysomnography, when more frequent than 15 per hour and associated with symptoms of sleep disturbance, the diagnosis of periodic limb movement disorder must be considered. However, periodic limb movement disorder may only be diagnosed in the absence of RLS symptoms so the diagnosis is not appropriate in this patient who identified, in retrospect, that she experiences sporadic but typical RLS symptoms characterized by the cardinal symptoms of RLS, which may be remembered by the acronym URGE (**u**ncomfortable **u**rge to move the legs, **r**est occurrence, **g**etting up or walking relieves symptoms, and **e**vening predominance).<sup>1,2</sup> While polysomnography is not necessary for the diagnosis of RLS, the provocative environment of the sleep laboratory (perhaps related to constraint by recording electrodes or stress of a foreign sleep environment) often illuminates a subtle clinical history of RLS in some patients, as in this case. Iron deficiency is associated with more intense RLS symptoms and evolution of augmentation<sup>3</sup> and should also be investigated in patients with mild symptoms, since iron replacement therapy alone may suffice as a primary treatment approach with sufficiently mild symptoms in lieu of dopamine agonist therapy or gabapentin. Causes of iron deficiency such as insufficient dietary intake, drug-adverse effects, or menstruation or occult gastrointestinal blood loss should be sought.

1. Trotti LM. Restless legs syndrome and sleep-related movement disorders. *Continuum (Minneapolis, Minn)* 2017;23(4 Sleep Neurology):1005–1016.
2. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group. International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med* 2014;15(8):860–873. doi:10.1016/j.sleep.2014.03.025.
3. Silber MH, Becker PM, Earley C, et al. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. *Mayo Clin Proc* 2013;88(9):977–986. doi:10.1016/j.mayocp.2013.06.016.



- 5. Which of the following medications is most likely to be associated with iron deficiency?

A. octreotide  
 B. ofloxacin  
 C. olmesartan  
 D. omeprazole  
 E. ondansetron

The preferred response is **D (omeprazole)**. Several medication classes can be associated with worsened RLS symptom intensity, including antidepressants, antihistamines, antiemetics, and antipsychotics. However, it has also been proposed that RLS might be associated indirectly with the use of proton pump inhibitors, which lower gastric acid and, subsequently, also lower iron absorption and serum iron levels.<sup>1,2</sup> A recently published study of patients without known risk factors for iron deficiency showed that use of proton pump inhibitors for more than 2 years was associated with an increased risk for development of subsequent iron deficiency, and that risk further increased with acid inhibition potency and decreased after discontinuation of acid pump inhibitors.<sup>1</sup> Further prospective evidence is needed to confirm the associations of iron deficiency, proton pump inhibitor therapy, and RLS symptoms.

1. Lam JR, Schneider JL, Quesenberry CP, Corley DA. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. *Gastroenterology* 2017;152(4):821–829.e.1. doi:10.1053/j.gastro.2016.11.023.
2. Smith HS, Dhingra R, Ryckewaert L, Bonner D. Proton pump inhibitors and pain. *Pain Physician* 2009;12(6):1013–1023.

The patient's serum ferritin is 8 ng/mL. She begins iron replacement therapy with ferrous fumarate 65 mg 3 times daily 1 hour before meals. She also had been receiving omeprazole for comorbid gastroesophageal reflux and began that drug about 3 years prior to onset of habitual RLS symptoms, and this was discontinued. In follow-up 2 months later, the patient states that she is tolerating nasal CPAP therapy well using a nasal pillow interface. Review of a compliance report downloaded from her CPAP device demonstrates 92% of nights with 4 hours or greater use for an average of 8 hours and 32 minutes. The 95th percentile CPAP pressure was 7.6 cm on her auto-titrating CPAP device, which had been set spanning the range of 5 cm H<sub>2</sub>O to 15 cm H<sub>2</sub>O. Her RLS symptoms have also essentially resolved.

She feels that her sleep quality has subjectively improved and is enriched. She reports that she can now remember dreams, which are sometimes vivid, for the first time in years. However, she reports no change in the degree of her daytime sleepiness, and a repeat Epworth Sleepiness Scale score was again elevated at 14, with a tendency to nap readily and doze whenever circumstances permit. No symptoms of cataplexy, hypnagogic hallucinations, or sleep paralysis are present.

- 6. Which of the following additional diagnostic evaluations would be most appropriate in evaluating the patient's symptoms of hypersomnolence?

A. home overnight oximetry  
 B. home sleep testing  
 C. maintenance of wakefulness test  
 D. multiple sleep latency test (MSLT)  
 E. polysomnography

The preferred response is **D (multiple sleep latency test [MSLT])**. This patient has persistent symptoms of significant daytime hypersomnolence, despite what appears to be adequate treatment of other probable causes or contributors such as sleep-disordered breathing and RLS. While additional formal assessment with polysomnography to confirm adequacy of sleep-disordered breathing treatment may have been considered, the patient's CPAP device download indicates excellent treatment adherence and response and suggests an adequate sleep schedule and duration. According to the American Academy of Sleep Medicine practice parameter, MSLT is indicated for the evaluation of narcolepsy and related primary central nervous system hypersomnia disorders such as idiopathic hypersomnia.<sup>1</sup> Mean sleep latencies under 8.0 minutes are considered indicative of excessive daytime sleepiness, and most patients with narcolepsy have mean sleep latencies below 5 minutes. Many sleep centers also routinely perform 1 or 2 weeks of wrist actigraphy monitoring preceding MSLT to ensure adequacy of sleep quantity and exclusion of insufficient sleep syndrome or a circadian disorder of misaligned sleep such as advanced or delayed sleep-wake phase disorders. At a minimum, a sleep diary to verify sufficient sleep quantity should be performed before MSLT, as insufficient amounts of sleep can create false-positive MSLT results even in individuals without primary hypersomnias. In preparation for MSLT, it is also necessary to consider discontinuing any confounding sedating or pain medications such as opiates at least 1 week prior to MSLT. Sedative drugs can confound interpretations of MSLT, leading to false-positive results. Additionally, other centrally active medications, especially antidepressants, stimulants, or benzodiazepines, should be discontinued for at least 1 to 2 weeks (and 4 to 6 weeks for some long-acting selective serotonin reuptake inhibitor [SSRI] medications such as fluoxetine) since these medications could suppress REM sleep (which may potentially lead to a false-negative MSLT) or could lead to REM sleep rebound following drug withdrawal, potentially leading to false-positive sleep-onset REM periods on MSLT if the study is done too soon following drug discontinuance. The maintenance of wakefulness test is useful for determining the response to stimulant and wake-promoting treatments for hypersomnia and in assessing the patient's ability to maintain wakefulness for driving or similar activities where safety is essential.<sup>2</sup>

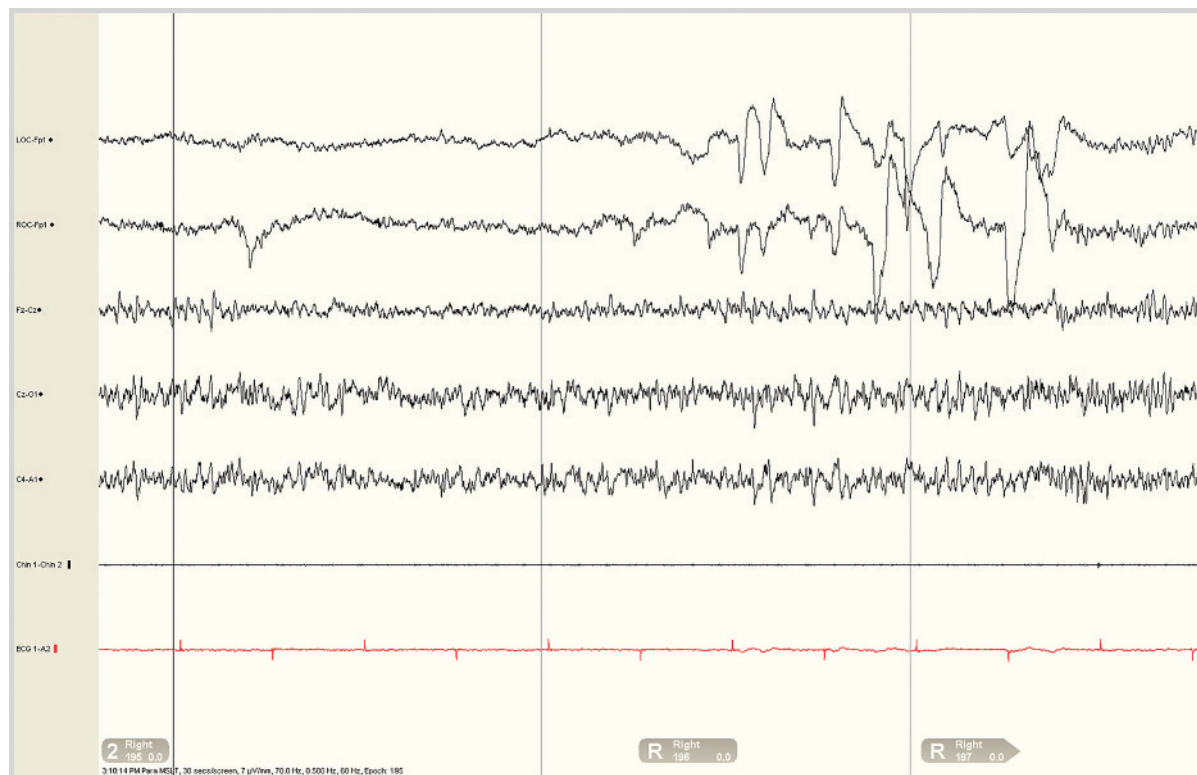
1. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28(1):113–121.

2. Wise MS. Objective measures of sleepiness and wakefulness: application to the real world? *J Clin Neurophysiol* 2006;23(1):39–49. doi:10.1097/01.wnp.0000190416.62482.42.

It is verified that the patient is not receiving any sedating medications or antidepressants. She is instructed to continue with CPAP therapy regularly, to continue sleeping at least 8 to 9 hours or longer each night, and to refrain from caffeine use 1 week prior to testing. Repeat polysomnography is also performed on the night prior to MSLT to confirm treatment adequacy for OSA and sleep-fragmenting periodic limb movements. This polysomnogram demonstrates reduced frequency of periodic leg movements of sleep at 18 per hour, with a periodic limb movement arousal index of 2 per hour. During this second polysomnogram, a full CPAP trial is performed, and CPAP titration is found effective at 8 cm H<sub>2</sub>O, her usual recent home treatment pressure. The following day, MSLT is performed with nap opportunities at 9:00 AM, 11:00 AM, 1:00 PM, and 3:00 PM. An example 30-second epoch from the patient's first nap is shown in **PMP Figure 2**.

*Continued on page 1200*

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## PMP FIGURE 2

Multiple sleep latency test showing a 30-second epoch. This example shows eye movements in the electrooculogram (channels 1–2), mixed-frequency EEG activity with saw-tooth waveforms (channels 3–5), and submental (chin) EMG atonia (channel 6).

► 7. Which of the following sleep stages is shown in the MSLT example in **PMP Figure 2**?

- A. REM sleep
- B. sleep stage N1
- C. sleep stage N2
- D. sleep stage N3
- E. wakefulness

The preferred response is **A (REM sleep)**. The MSLT epoch shown in **PMP Figure 2** shows clear rapid eye movements in the electrooculography channels, a relatively low-voltage EEG pattern with saw-tooth waveforms, and submental EMG atonia, which are features consistent with REM sleep.<sup>1</sup> Entry into REM sleep within 15 minutes of the first epoch of sleep during a nap defines a sleep-onset REM period during MSLT. Two or more sleep-onset REM periods are considered abnormal and supportive of a diagnosis of narcolepsy, together with a short mean sleep latency of under 8.0 minutes. Wake stage would demonstrate a background alpha rhythm and generally shows faster EEG rhythms and greater EMG tone, with additional features of eye blinks and muscle and movement artifact. N1 sleep is characterized by predominantly slower EEG rhythms in the theta frequency range and slow rolling eye movements on electrooculography. The hallmarks of N2 sleep are K complexes and sleep spindles with under 20% of the 30-second epoch containing high-voltage (75 uV or greater amplitude) delta slow waves, whereas N3 is composed of more than 20% (6 or more seconds) of high-voltage delta EEG activity.

1. Berry RB, Brooks R, Gamaldo CE, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Version 2.2. Darien, IL: American Academy of Sleep Medicine, 2015.

During the MSLT, the patient falls asleep rapidly during each of the four naps, with individual sleep latencies of 2.5, 1.5, 3.0, and 4.0 minutes, yielding a mean sleep latency of 2.8 minutes. There are three sleep-onset REM periods (0 or 1 being normal). The MSLT findings of a short sleep latency (fewer than 8.0 minutes) and two or more sleep-onset REM periods are supportive of a clinical diagnosis of narcolepsy type 2 given that she does not experience cataplexy. She has no history of hypnagogic hallucinations or sleep paralysis.

- 8. Which of the following psychostimulant/wake-promoting agents is the best choice for the initial treatment of hypersomnia in this patient?
- A. bupropion
  - B. lisdexamfetamine
  - C. methamphetamine
  - D. methylphenidate
  - E. modafinil

The preferred response is E (**modafinil**). Of the wake-promoting agents and psychostimulants listed, modafinil has the best evidence basis for the treatment of hypersomnia in narcolepsy and is indicated for the treatment of narcolepsy in the United States.<sup>1</sup> In fact, in this case, some experts may have reasonably argued that modafinil could have been used empirically for adjunctive treatment of hypersomnia once CPAP had been optimized, as ample evidence and indication for its use exist in the setting of adjunctive treatment of hypersomnia associated with OSA.<sup>2</sup> Each of the other stimulants listed (methylphenidate, methamphetamine, and lisdexamfetamine) are also useful in some narcolepsy cases, especially in those patients who do not respond to modafinil or cannot afford it. Typically, modafinil is begun at a dose of 100 mg or 200 mg in the morning, with a repeat dose at noon or 1:00 PM if wearing off of efficacy occurs, or it can be given in doses up to 300 mg to 400 mg in the morning if lower doses are ineffective. Women of childbearing potential need to be cautioned about potential interaction with estrogenic hormonal contraceptives, since these may be rendered less effective when modafinil is used in combination, and the additional use of barrier contraceptive methods should be recommended, along with folic acid.

1. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;30(12):1705–1711.
2. Avellar AB, Carvalho LB, Prado GF, Prado LB. Pharmacotherapy for residual excessive sleepiness and cognition in CPAP-treated patients with obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Sleep Med Rev* 2016;30:97–107. doi:10.1016/j.smrv.2015.10.005.

The patient is started on modafinil with titration to 400 mg each morning and experiences markedly improved alertness. With combined CPAP, iron replacement, and stimulant therapy, alertness is satisfactory, and she no longer dozes as often, remains alert while driving, and reports an Epworth Sleepiness Scale score of just 10 at her 3-month follow-up. However, her symptoms of fatigue persist, and her Fatigue Severity Scale rating is 54 (score is elevated with a cutoff of 39).

Concomitant to her sleep workup, she also notes increased muscle aching and worsening weakness that she has experienced over the last year prior to presentation. While having some degree of lifelong weakness, she also began noting more recent difficulties rising from a squatting position, and she notes more recent problems climbing stairs.

EMG demonstrates low-amplitude compound muscle action potentials (CMAPs), abnormal spontaneous activity with fibrillation potentials and myotonic discharges, and myopathic features of rapid recruitment of short duration and small motor unit potentials in proximal muscles. She notes some mild shortness of breath on exertion, but no orthopnea or paroxysmal nocturnal dyspnea. Pulmonary functions show a mildly reduced vital capacity of 2.16 cm<sup>3</sup>, with reduced maximal inspiratory and expiratory pressures between 36% and 60% of expected values. Arterial blood gas confirmed normocapnia with P<sub>a</sub>CO<sub>2</sub> of 38 torr.

- 9. Considering this patient's mild proximal muscle weakness, myalgias, and sleep disturbances, which of the following underlying associated myopathies is the most likely diagnosis?
- A. Duchenne muscular dystrophy
  - B. facioscapulohumeral muscular dystrophy
  - C. inclusion body myositis
  - D. myotonic dystrophy type 1
  - E. myotonic dystrophy type 2

The preferred response is **E (myotonic dystrophy type 2)**. Myotonic dystrophy is the most common form of muscular dystrophy seen in adult patients. Myotonic dystrophy is characterized by progressive weakness, variable clinical features of myotonia, and systemic multiorgan system manifestations. Two forms of myotonic dystrophy are recognized, with overlapping manifestations, although clinical and genetic distinctions exist. Myotonic dystrophy type 1 is a trinucleotide repeat expansion in the *DMPK* gene on chromosome 19, and myotonic dystrophy type 2 is instead caused by tetranucleotide expansion on chromosome 3 in the *CNBP* (*ZNF9*) gene.<sup>1,2</sup> While both types of myotonic dystrophy have myopathy, myotonia, hair loss, cataracts, diabetes mellitus type 2, testicular failure in men, and variable cardiac involvement, myotonic dystrophy type 2 (previously known as proximal myotonic myopathy) most often impacts proximal muscles and has initially mild weakness and often has clinically covert but electrophysiologically manifest myotonia. Both types of myotonic dystrophy may have prominent sleep disturbances and comorbidities, including central hypersomnia, obstructive and central sleep apnea, sleep-related hyperventilation, prominent RLS symptoms, and parasomnias.<sup>2–5</sup> Positive pressure therapy, including noninvasive positive pressure ventilation, may be an important part of the management of these patients, and many require adjunctive stimulant therapy to improve daytime alertness, functioning, and quality of life.<sup>2–3</sup> In this case, no evidence for sleep-related hypoventilation or hypercapnia is present to suggest the need for conversion from CPAP modality to bilevel positive airway pressure (biPAP) nocturnal ventilation.

1. Meola G, Cardani R. Myotonic dystrophy type 2: an update on clinical aspects, genetic and pathomolecular mechanism. *J Neuromuscul Dis* 2015;2(s2):S59–S71. doi:10.3233/JND-150088.
2. Fermin AM, Afzal U, Culebras A. Sleep in neuromuscular diseases. *Sleep Med Clin* 2016;11(1):53–64. doi:10.1016/j.jsmc.2015.10.005.
3. Irfan M, Selim B, Rabinstein AA, St Louis EK. Neuromuscular disorders and sleep in critically ill patients. *Crit Care Clin* 2015;31(3):533–550. doi:10.1016/j.ccc.2015.03.007.
4. Shepard P, Lam EM, St Louis EK, Dominik J. Sleep disturbances in myotonic dystrophy type 2. *Eur Neurol* 2012;68(6):377–380. doi:10.1159/000342895.
5. Lam EM, Shepard PW, St Louis EK, et al. Restless legs syndrome and daytime sleepiness are prominent in myotonic dystrophy type 2. *Neurology* 2013;81(2):157–164. doi:10.1212/WNL.0b013e31829a340f.

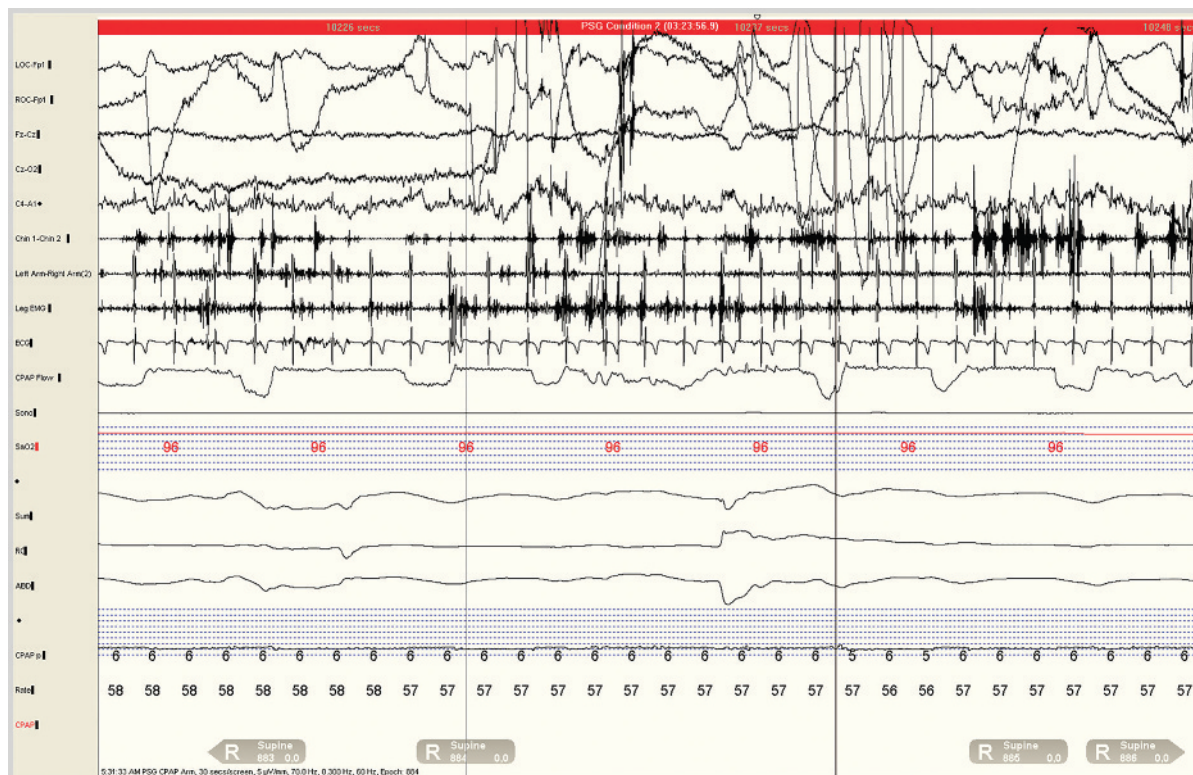
The gene test for myotonic dystrophy type 2 is positive with 6600 CCTG repeats, and she is diagnosed with myotonic dystrophy type 2. For the next year, she does well on a combination of CPAP therapy, iron replacement, and modafinil and reports an improved level of sleepiness of only 8 on the Epworth Sleepiness Scale. At 1-year follow-up, additional collateral history from her husband indicates that since her last visit, she has experienced the onset of new peculiar behaviors during sleep, involving complex motor behaviors that usually occur in the second half of the night. She frequently vocalizes and has either knitting-type movements of the hands (which is one of her daytime hobbies) or, on some occasions, flailing or punching arm movements paralleling recalled dream mentation of being chased by a bear or persons.

Evolution of the new nocturnal behaviors prompt further review of her previous polysomnogram, and a representative epoch is shown in **PMP Figure 3**.

*Continued on page 1203*



Continued from page 1202



### PMP FIGURE 3

Polysomnogram showing a 30-second epoch. This epoch shows excessive phasic muscle activity bursts in the chin, arm, and leg EMG (channels 6–8). Characteristic rapid eye movement (REM) sleep features include rapid eye movements in the electrooculogram (channels 1–2) and relatively desynchronized mixed-frequency EEG activity (channels 3–5).

- 10. Which of the following findings is evident in the polysomnogram REM sleep epoch shown in **PMP Figure 3**?
- abnormal eye movements
  - alternating leg movement activation
  - atonia loss
  - normal atonia
  - periodic leg movements

The preferred response is **C (atonia loss)**. The epoch in **PMP Figure 3** shows REM sleep atonia loss (also known as REM sleep without atonia). REM sleep atonia loss may be seen in patients without parasomnias as an apparently incidental or isolated finding on polysomnography (similar to the finding of periodic leg movements of sleep during non-REM sleep in a patient without RLS) or also in association with antidepressant use, but it is more frequent in patients with REM sleep behavior disorder (RBD) and is distinguishable from patients with OSA syndrome.<sup>1-4</sup> Quantitative analysis of REM sleep without atonia showed the following percentages of REM sleep muscle activity in this patient's case: submental phasic muscle activity 32% (normal less than 15.5%), anterior tibialis phasic muscle activity 52% (normal less than 30.2%), combined submental and anterior tibialis phasic

muscle activity 44% (normal less than 37.8%), and tonic muscle activity 4.6% (normal less than 1.2%).<sup>2</sup> Polysomnographic REM sleep without atonia is required for the diagnosis of RBD and helps differentiate RBD from non-REM sleep parasomnias and other nocturnal events such as nocturnal frontal lobe epilepsy. This patient has evolved a clinical history of complex motor behavior paralleling dream mentation that is clearly consistent with dream enactment, and on further review of her previous polysomnogram, she had already had REM sleep without atonia, which had eluded attention before in the absence of clinical symptoms. Her dream enactment symptoms together with polysomnographic REM sleep without atonia now fulfill the diagnostic criteria for RBD. Recent evidence suggests that approximately 14% of patients with isolated/incidental REM sleep without atonia may later develop RBD during longitudinal follow-up, as in this patient, although further larger longitudinally followed cohorts will be necessary to confirm this risk.<sup>3</sup>

1. Frauscher B, Iranzo A, Gaig C, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. *Sleep* 2012;35(6):835–847. doi:10.5665/sleep.1886.
2. McCarter SJ, St Louis EK, Duwell EJ, et al. Diagnostic thresholds for quantitative REM sleep phasic burst duration, phasic and tonic muscle activity, and REM atonia index in REM sleep behavior disorder with and without comorbid obstructive sleep apnea. *Sleep* 2014;37(10):1649–1662. doi:10.5665/sleep.4074.
3. Stefani A, Gabelia D, Högl B, et al. Long-term follow-up investigation of isolated rapid eye movement sleep without atonia without rapid eye movement sleep behavior disorder: a pilot study. *J Clin Sleep Med* 2015;11(11):1273–1279. doi:10.5664/jcsm.5184.
4. McCarter SJ, St Louis EK, Sandness DJ, et al. Antidepressants increase REM sleep muscle tone in patients with and without REM sleep behavior disorder. *Sleep* 2015;38(6):907–917. doi:10.5665/sleep.4738.

The patient is diagnosed with REM sleep behavior disorder (RBD) and is prescribed clonazepam 0.5 mg nightly at bedtime. At 2-month follow-up, her husband reports that the patient continues to manifest violent dream enactment behaviors at least twice weekly, with punching, kicking, and screaming paralleling nightmarish dream content. Despite further titration of clonazepam to 2.0 mg nightly, behaviors continue, and she has had one fall from bed, which bruised her arm, and has punched her husband on another occasion as she dreamt she was being attacked by a bear. She also reported worsened daytime sedation and mild unsteadiness.

- 11. Which of the following treatments should be considered in view of the patient's continued dream enactment?
- A. carbamazepine
  - B. donepezil
  - C. melatonin
  - D. pramipexole
  - E. ramelteon

The preferred response is **C (melatonin)**. The evidence base remains limited for the best treatment options for RBD.<sup>1</sup> Since RBD is a potentially injurious parasomnia, safety counseling is important for all patients. Patients with RBD should be advised to consider lowering their mattress to the floor in case of falls or placing additional mattresses or cushions near the bed and removing sharp-cornered furniture or other potentially injurious hazards from the bedside. Firearms or other weapons should be removed from the bedroom environment. Melatonin and clonazepam are the two most commonly used treatments to prevent injury in RBD.<sup>1–3</sup> Clonazepam has been considered the traditional treatment of choice for RBD based on clinical experience and large retrospective reports. Of the choices listed, melatonin has the best evidence, supported by one small double-blind, placebo-controlled randomized crossover study,<sup>4</sup> as well as large retrospective case series evidence.<sup>2</sup> The most common adverse effects of melatonin reported by patients with RBD include dizziness, trouble thinking, unsteadiness, nausea, and sexual dysfunction.<sup>2</sup> Melatonin is often more tolerable than clonazepam and overall appears to have comparable or possibly superior efficacy for prevention of injury.<sup>2</sup> The average effective dosage for treatment of RBD appears to be 6.0 mg nightly, which is typically given at bedtime.<sup>2</sup> For patients with violent sleep behaviors who continue to be refractory to clonazepam, melatonin, and other pharmacotherapies, or who are intolerant to medication side effects, the use of a bed alarm system has also been reportedly effective for prevention of injurious attacks in RBD.<sup>5</sup>

1. Jung J, St Louis EK. Treatment of REM sleep behavior disorder. *Curr Treat Options Neurol* 2016;18(11):50. doi:10.1007/s11940-016-0433-2.
2. McCarter SJ, Boswell CL, St Louis EK, et al. Treatment outcomes in REM sleep behavior disorder. *Sleep Med* 2013;14(3):237–242. doi:10.1016/j.sleep.2012.09.018.
3. McGrane IR, Leung JG, St Louis EK, Boeve BF. Melatonin therapy for REM sleep behavior disorder: a review of evidence. *Sleep Med* 2015;16(1):19–26. doi:10.1016/j.sleep.2014.09.011.
4. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res* 2010;19(4):591–596. doi:10.1111/j.1365-2869.2010.00848.x.c
5. Howell MJ, Arneson PA, Schenck CH. A novel therapy for REM sleep behavior disorder (RBD). *J Clin Sleep Med* 2011;7(6):639A–644A. doi:10.5664/jcsm.1470.

Since clonazepam had been ineffective at doses of 2.0 mg nightly, the patient is started on melatonin 3 mg nightly, but because of continued sporadic violent behaviors at 6-month follow-up, melatonin is further titrated to 6 mg nightly, with a substantial decrease in the frequency of her dream enactment behaviors. Further longitudinal follow-up annually over 5 years shows no further evolution of new neurologic symptoms or signs.

- 12. This patient's parasomnia diagnosis suggests heightened risk for future development of which of the following neurologic diagnoses?
- A. IgLON5 autoimmunity
  - B. multiple sclerosis
  - C. Parkinson disease
  - D. pontine astrocytoma
  - E. Wilson disease

The preferred response is **C (Parkinson disease)**. RBD has an especially strong association with concurrent or eventual future phenoconversion to a defined synucleinopathy neurodegenerative disease.<sup>1–6</sup> Idiopathic RBD in an adult is currently thought by most experts to represent a prodromal form of synucleinopathy. Longitudinal cohort studies of patients with idiopathic RBD have demonstrated a very strong association with the future development of a defined neurodegenerative disease, predominantly Parkinson disease, nonamnesic mild cognitive impairment, dementia with Lewy bodies, and multiple system atrophy. The risk of phenoconversion over a 2 to 5 year interval following diagnosis is approximately 15% to 35%, while long-term follow-up over 6 to 25 years suggests that phenoconversion may be much higher, in the broad range of 40% to 91.9%.<sup>2,3</sup> The phenoconversion risk is greater over longer periods of follow-up, although progression is highly variable among individuals, and factors defining the risk for phenoconversion are not yet well defined, although other “soft signs” of synucleinopathy, such as anosmia and color vision deficits, are suggestive of a higher risk toward phenoconversion. The largest pathologic series of patients with RBD demonstrated that 94% of those with neurodegenerative disorders had synucleinopathy.<sup>4</sup> Patients should be counseled about the risk and the need for longitudinal neurologic follow-up to monitor for symptoms and signs of evolving parkinsonism, cognitive, or autonomic impairments, so that they may receive early symptomatic treatment and, eventually, future neuroprotective therapies.

1. Postuma RB, Gagnon JF, Vendette M, et al. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology* 2009;72(15):1296–1300. doi:10.1212/01.wnl.0000340980.19702.6e.
2. Iranzo A, Fernández-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One* 2014;9(2):e89741. doi:10.1371/journal.pone.0089741.
3. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med* 2013;14(8):744–748. doi:10.1016/j.sleep.2012.10.009.

4. Boeve BF, Silber MH, Ferman TJ, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med* 2013;14(8):754–762. doi:10.1016/j.sleep.2012.10.015.
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This case exemplifies several important principles in sleep neurology practice. First, sleepiness and fatigue are common symptoms in patients with neurologic disorders, and the Epworth Sleepiness Scale is a helpful bedside tool to enable recognition of significant symptoms of daytime sleepiness that may signify the need to consider whether an underlying primary sleep disorder exists. Second, sleep medicine patients frequently have multiple overlapping symptoms of sleep disturbance, requiring a logical, sequential approach to effectively distinguish different sleep disorders that require specific therapeutic approaches. In this patient, the initial approach was to distinguish two diagnoses impacting sleep quality using polysomnography, OSA and RLS, requiring treatment by nasal CPAP and iron replacement therapy. Second, after symptoms of sleepiness persisted, an underlying narcolepsy type 2 diagnosis, suggested by her history of lifelong sleepiness, was supported by MSLT evaluation. Third, continued symptoms of daytime tiredness persisted following combined CPAP, iron, and stimulant therapy with modafinil, suggesting prominent fatigue accompanying another neurologic disorder causing proximal weakness, which proved to be myotonic dystrophy type 2. Last, the importance of longitudinal follow-up was demonstrated by evolution of dream enactment behavior and subsequent diagnosis of RBD, which necessitates further longitudinal follow-up to guide treatment for injury prevention and enable monitoring and treatment for symptoms and signs of synucleinopathy. Sleep neurology includes a myriad of fascinating diagnostic considerations, requiring broad interdisciplinary clinical, neurophysiology, and pharmacologic management expertise, and the possibility of improving functioning and quality of life for our patients.<sup>1</sup>

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Page numbers in **boldface** type indicate major discussions. Letters after page numbers refer to the following: c = case study; f = figure; r = reference; t = table.

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# Sleep Neurology

## List of Abbreviations

AAA	American Automobile Association	ICD-10	<i>International Classification of Diseases, Tenth Revision</i>
AAMVA	American Association of Motor Vehicle Administrators	ICD-10-CM	<i>International Classification of Diseases, Tenth Revision, Clinical Modification</i>
AAN	American Academy of Neurology	ICSD-3	<i>International Classification of Sleep Disorders, Third Edition</i>
AASM	American Academy of Sleep Medicine	IV	Intravenous
AD	Alzheimer disease	IVIg	Intravenous immunoglobulin
AHI	Apnea-hypopnea index	MRI	Magnetic resonance imaging
ALS	Amyotrophic lateral sclerosis	MSA	Multiple system atrophy
BiPAP	Bilevel positive airway pressure	MSLT	Multiple sleep latency test
BMI	Body mass index	MWT	Maintenance of wakefulness test
CBT-I	Cognitive-behavioral therapy for insomnia	NHTSA	National Highway Traffic Safety Administration
CDC	Centers for Disease Control and Prevention	NIV	Noninvasive ventilation
CMS	Centers for Medicare and Medicaid Services	NMDA	<i>N</i> -methyl-D-aspartate
CPAP	Continuous positive airway pressure	nPAP	Nasal positive airway pressure
CPT	<i>Current Procedural Terminology</i>	OSA	Obstructive sleep apnea
CSA	Central sleep apnea	PAP	Positive airway pressure
CSF	Cerebrospinal fluid	PD	Parkinson disease
DLB	Dementia with Lewy bodies	PET	Positron emission tomography
DSM-5	<i>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</i>	PLM	Periodic limb movement
ECG	Electrocardiogram	PLMS	Periodic limb movements of sleep
EEG	Electroencephalogram	RBD	Rapid eye movement sleep behavior disorder
EMG	Electromyogram/electromyography	REM	Rapid eye movement
FDA	US Food and Drug Administration	RLS	Restless legs syndrome
FDG-PET	Fludeoxyglucose positron emission tomography	SCOPA-S	Scales for Outcomes in Parkinson Disease Sleep Scale
FMCSA	Federal Motor Carrier Safety Administration	SINBAR	Sleep Innsbruck Barcelona [group]
GABA	$\gamma$ -Aminobutyric acid	SNRI	Serotonin norepinephrine reuptake inhibitor
GABA-ergic	$\gamma$ -Aminobutyric acid-mediated	SPECT	Single-photon emission computed tomography
H1N1	Influenza A	SSRI	Selective serotonin reuptake inhibitor
HLA	Human leukocyte antigen	VNS	Vagus nerve stimulation
ICD-9-CM	<i>International Classification of Diseases, Ninth Revision, Clinical Modification</i>		